Biopharmaceutical Sector

Weekly Update – May 13, 2024

STIFEL | Healthcare

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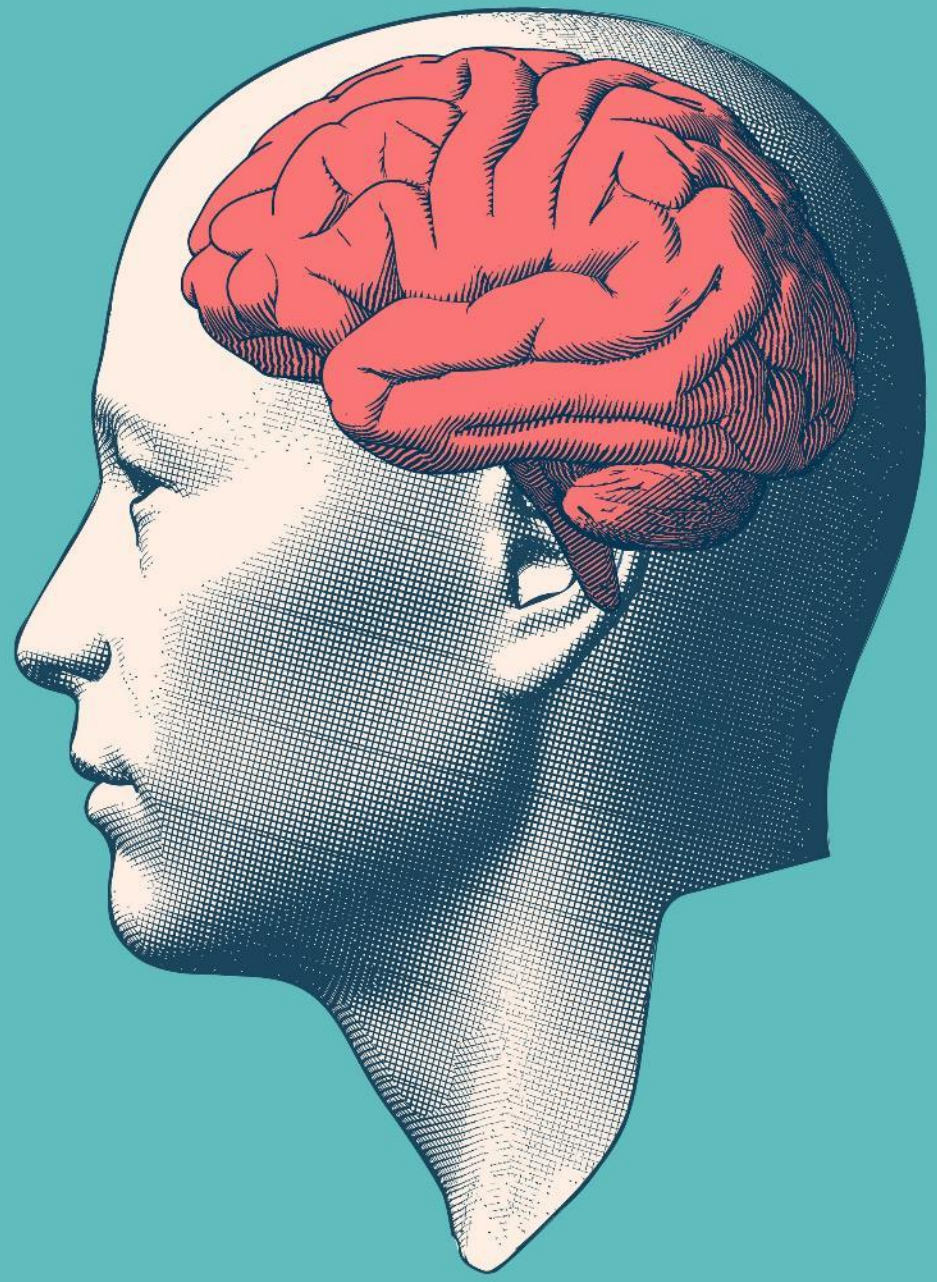

STIFEL | Healthcare

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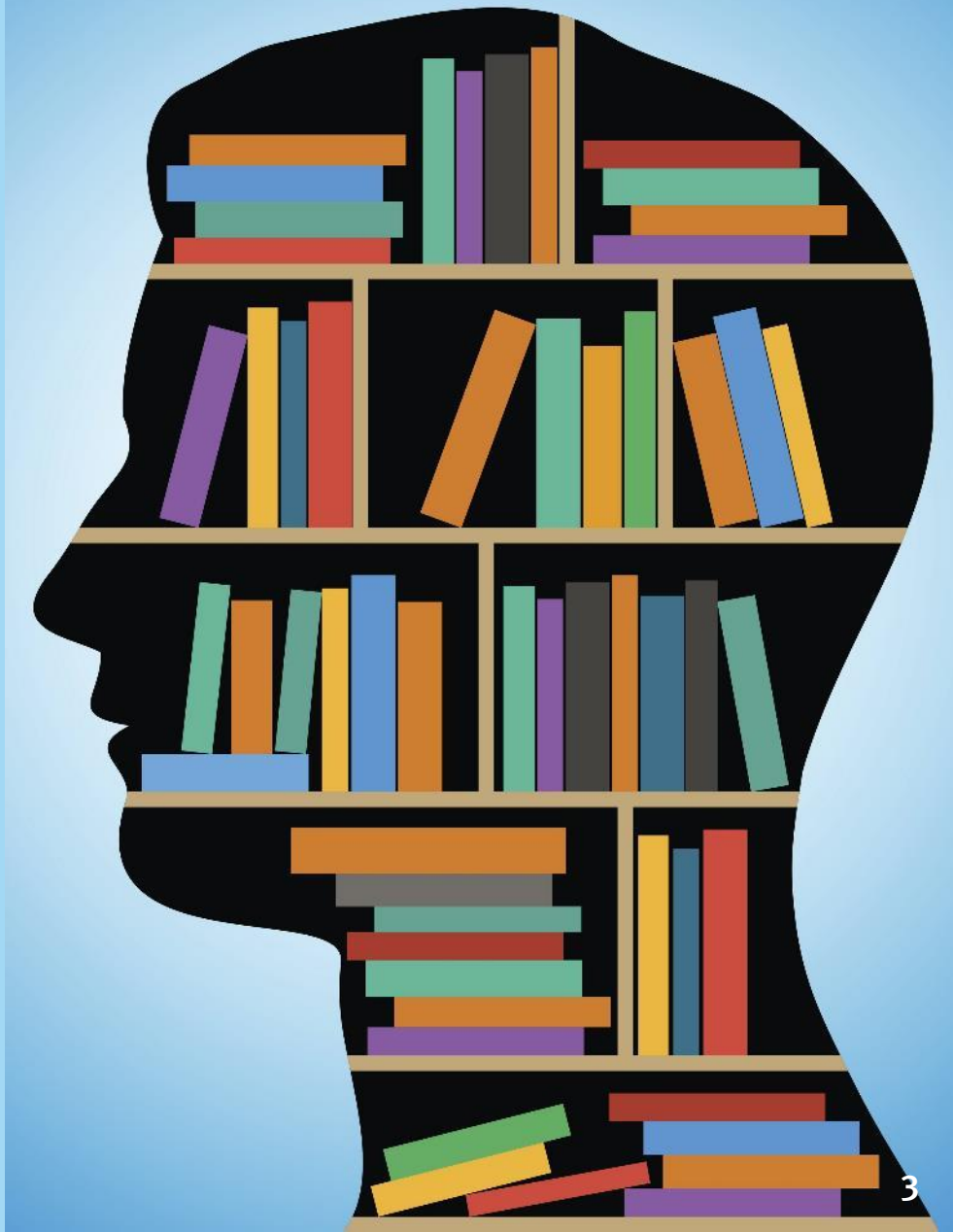
Accessing Past Issues

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

May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 15, 2024 (FDA Commissioner Priorities)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)



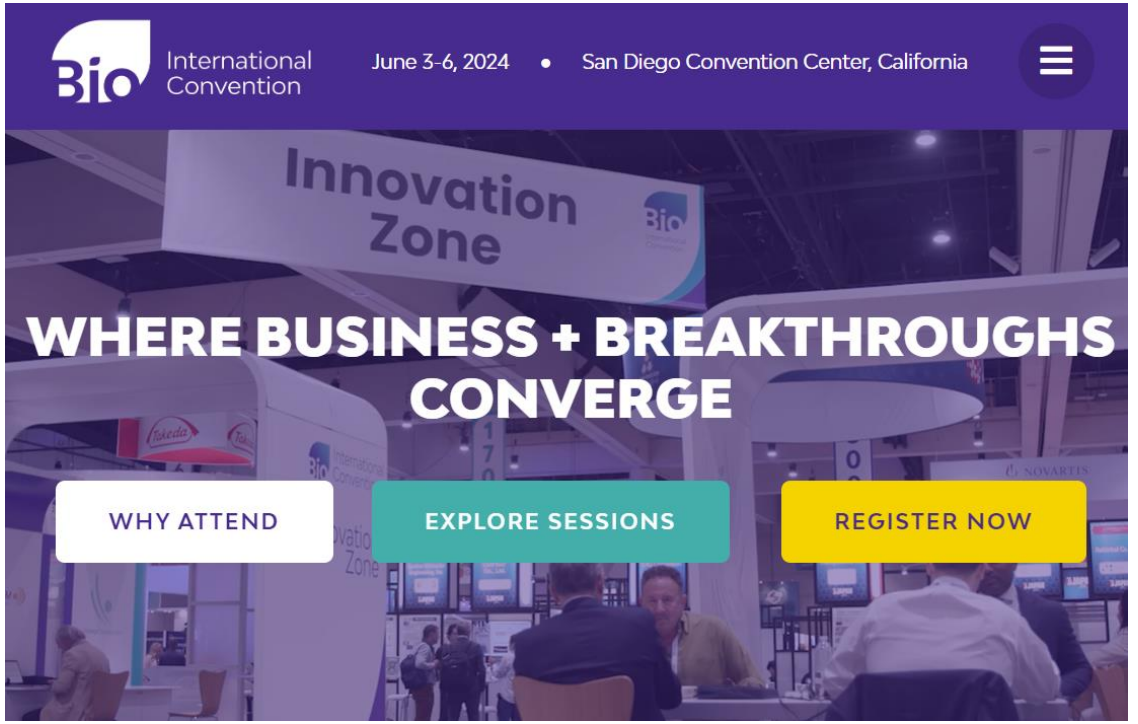
Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on May 10, 2024.

The next event will be on May 17, 2024.

Please join us.

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



Please join us at BIO on June 3 to 6, 2024.

For details on attending please go to:
https://convention.bio.org/

We will also be at ASCO from May 31 to June 2nd. Happy to meet up there as well.

Feel Free to Meet us At BioEquity This Week

Also, Feel Free to Meet us At ASCO in Three Weeks

To meet us at ASCO please contact Natasha Yeung (yeungn@stifel.com) to set up a meeting.

Stifel will be hosting a cocktail event at the conference.

Macroeconomics Update

Representation of Firing Neuron by Koto Feja

Consumer Sentiment Tumbles as Inflation Fears Surge

Jeff Cox, *CNBC*, May 10, 2024 (excerpt)

Consumer sentiment slumped as inflation expectations rose, despite otherwise strong signals in the economy, according to a closely watched survey released Friday.

The University of Michigan Survey of Consumers sentiment index for May posted an initial reading of 67.4 for the month, down from 77.2 in April and well off the Dow Jones consensus call for 76. The move represented a one-month decline of 12.7% but a year-over-year gain of 14.2%.

Along with the downbeat sentiment measure, the outlook for inflation across the one- and five-year horizons increased. The one-year outlook jumped to 3.5%, up 0.3 percentage point from a month ago to the highest level since November.

Also, the five-year outlook rose to 3.1%, an increase of just 0.1 percentage point but reversing a trend of lower readings in the past few months, also to the highest since November.

“While consumers had been reserving judgment for the past few months, they now perceive negative developments on a number of dimensions,” said Joanne Hsu, the survey’s director. “They expressed worries that inflation, unemployment and interest rates may all be moving in an unfavorable direction in the year ahead.”

Source: https://www.cnbc.com/2024/05/10/consumer-sentiment-tumbles-as-inflation-fears-surge-closely-watched-survey-shows.html

Bowman Sees Fed On Hold While Inflation Lingers

Steve Matthews, *Bloomberg*, May 10, 2024 (excerpt)

Federal Reserve Governor Michelle Bowman said she doesn't expect it will be appropriate for the Fed to cut interest rates in 2024, pointing to persistent inflation in the first several months of the year.

Bowman made the comments in a Bloomberg News interview following a speech to bankers in Texas, where she urged the central bank to proceed "carefully and deliberately" as policymakers move toward the Fed's 2% inflation goal.

"I, at this point, have not written in any cuts" for 2024, Bowman said in the interview, referring to the economic projections officials submit each quarter. "I've sort of had an even expectation of staying where we are for longer. And that continues to be my base case."

A series of policymakers this week have echoed calls for higher-for-longer rates. Dallas Fed President Lorie Logan, speaking in New Orleans Friday, said "it's just too early to think about cutting rates," given disappointing inflation data so far this year.

Chicago Fed President Austan Goolsbee said he doesn't see much evidence inflation is stuck above the Fed's target, but was reluctant to say when rate cuts might be appropriate.

"It doesn't make sense to be tying our hands, even partly, when we know we're going to get tons of data," he said at an event Friday hosted by the Economic Club of Minnesota.

Source: https://www.bloomberg.com/news/articles/2024-05-10/bowman-says-fed-should-move-carefully-to-reach-inflation-goal

Miki Bowman, Governor, Federal Reserve

Wall Street Closes Up, Another Weekly Gain Ahead of Inflation Data

Stephen Culp, *Reuters*, May 10, 2024 (excerpt)

U.S. stocks eked out modest gains on Friday and all three indexes posted another weekly advance as investors parsed comments from Federal Reserve officials and looked ahead to crucial inflation data next week.

The S&P 500 and the Dow were modestly higher and the Nasdaq ended essentially unchanged. All three indexes were up for the week with the blue-chip Dow nabbing its largest Friday-to-Friday percentage advance since mid-December.

Commentary from several Fed officials helped set expectations as market participants looked toward next week's inflation data. "Nobody really wants to take a big position prior to next week," said Chuck Carlson, chief executive officer at Horizon Investment Services in Hammond, Indiana. "And we're getting into a time of year where people seem to slip out early on Fridays."

"The biggest story is the decline in Consumer Sentiment, but outside of that there isn't much to hang your hat on," Carlson added.

Analysts expect the crucial CPI report to show underlying "core" price inflation of 3.6% year-on-year, which would be the coolest reading in over three years.

"The Fed is geared not to raise rates but cut them, so 'higher for longer' is about as dire as it's going to unless things really fall off the table," said Paul Nolte, senior wealth advisor & market strategist at Murphy & Sylvest in Elmhurst, Illinois.

Source: https://www.reuters.com/markets/us/futures-rise-ahead-data-speeches-fed-officials-2024-05-10/

Biopharma Market Update

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

The XBI Closed at 88.14 Last Friday (May 10), Down 2% for the Week

The XBI was flat last week in the absence of new economic data. The S&P 500 rose. Next week's CPI number will be a critical driver of the biotech market in the weeks and months ahead. The Stifel global biotech market barometer fell by 5.7% last week.

Biotech Stocks Down Last Week

Return: May 4 to May 10, 2024

Nasdaq Biotech Index: -1.1%
Arca XBI ETF: -2.0%
Stifel Global Biotech EV (adjusted): -5.7%*
S&P 500: +1.9%

Return: Dec 29, 2023 to May 10, 2024 (YTD)

Nasdaq Biotech Index: -1.0%
Arca XBI ETF: -1.3%
Stifel Global Biotech EV (adjusted): +17.6%*
S&P 500: +9.5%

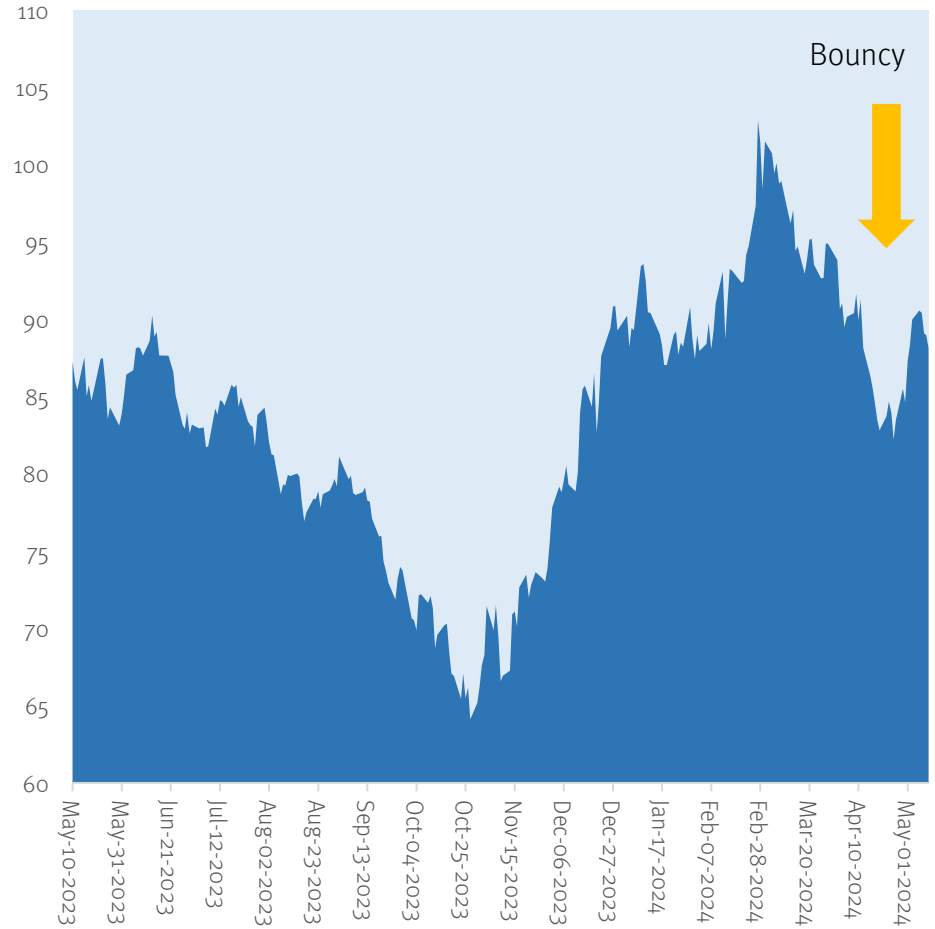
VIX Down Further

Jan 20, 2023: 19.9%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
Apr 26, 2024: 15.0%
May 3, 2024: 13.5%
May 10, 2024: 12.6%

10-Year Treasury Yield Flat

Jan 20, 2023: 3.48%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
Apr 26, 2024: 4.66%
May 3, 2024: 4.5%
May 10, 2024: 4.5%

XBI, May 10, 2023 to May 10, 2024



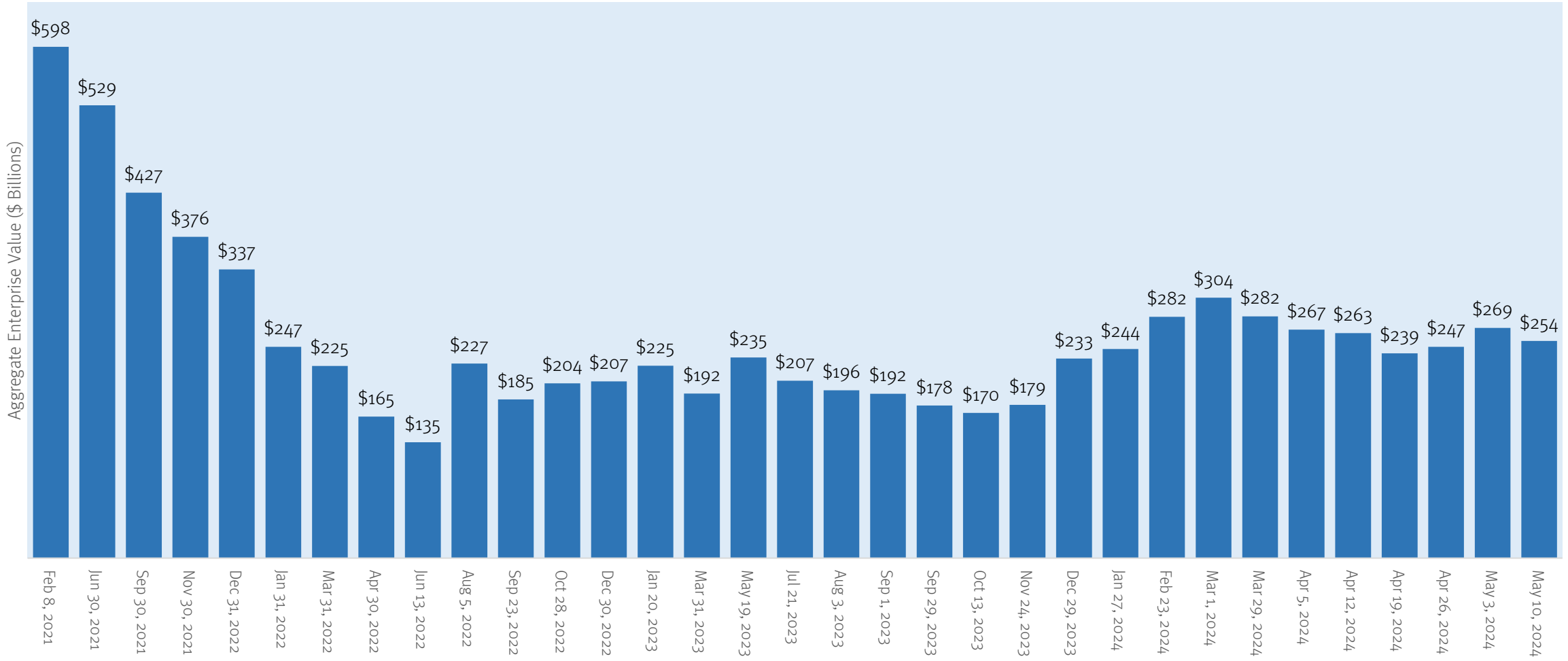
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Down 5.7% Last Week

Biotech stocks fell last week as investor nerves ahead of inflation data took its toll. On an exit/addition adjusted basis biotech is up 17% for the year. While the recent downturn has impacted the sector, a robust rally has unfolded in 2024.

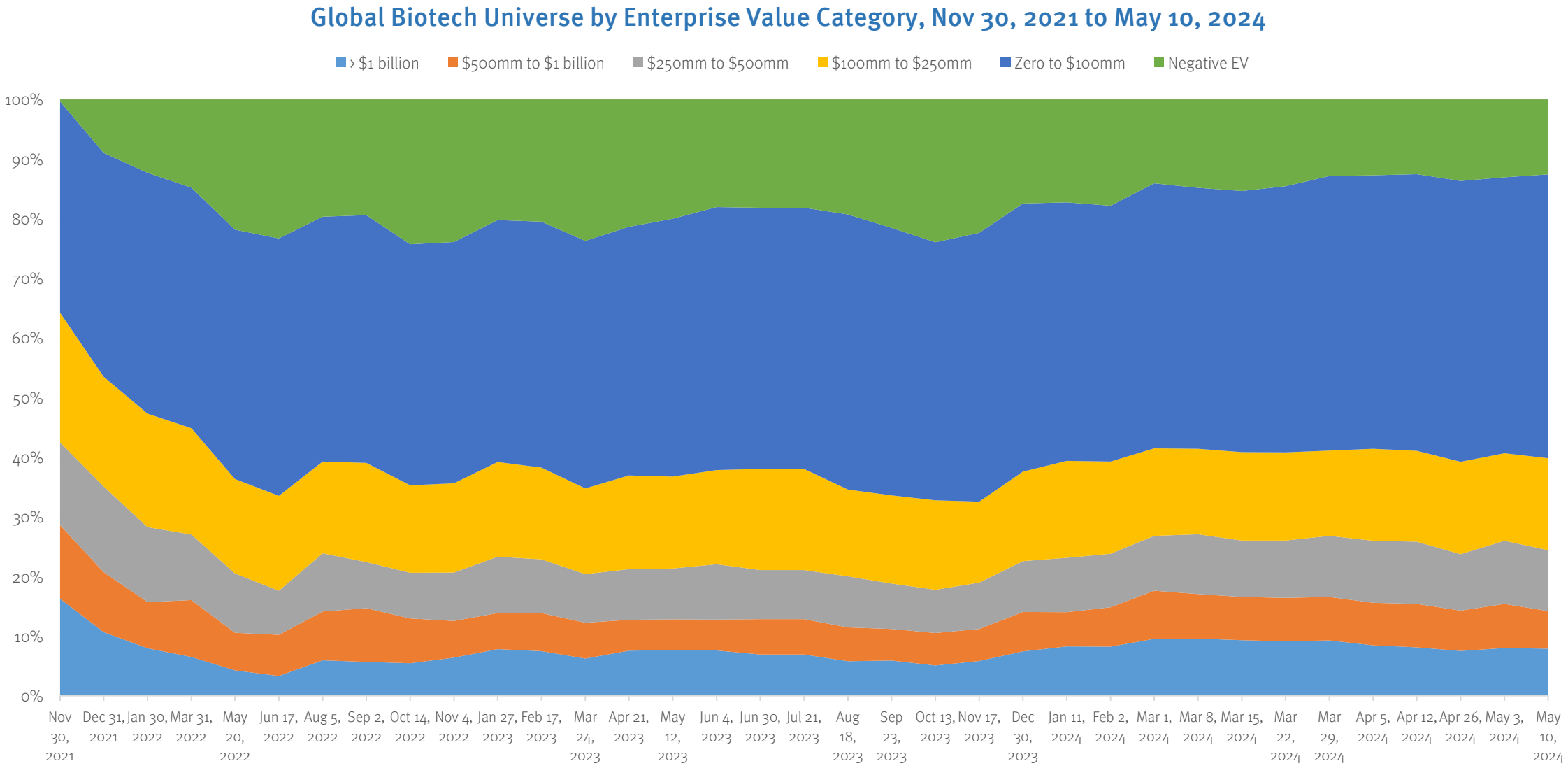
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to May 10, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

The population of companies worth less than $100mm expanded substantially last week.

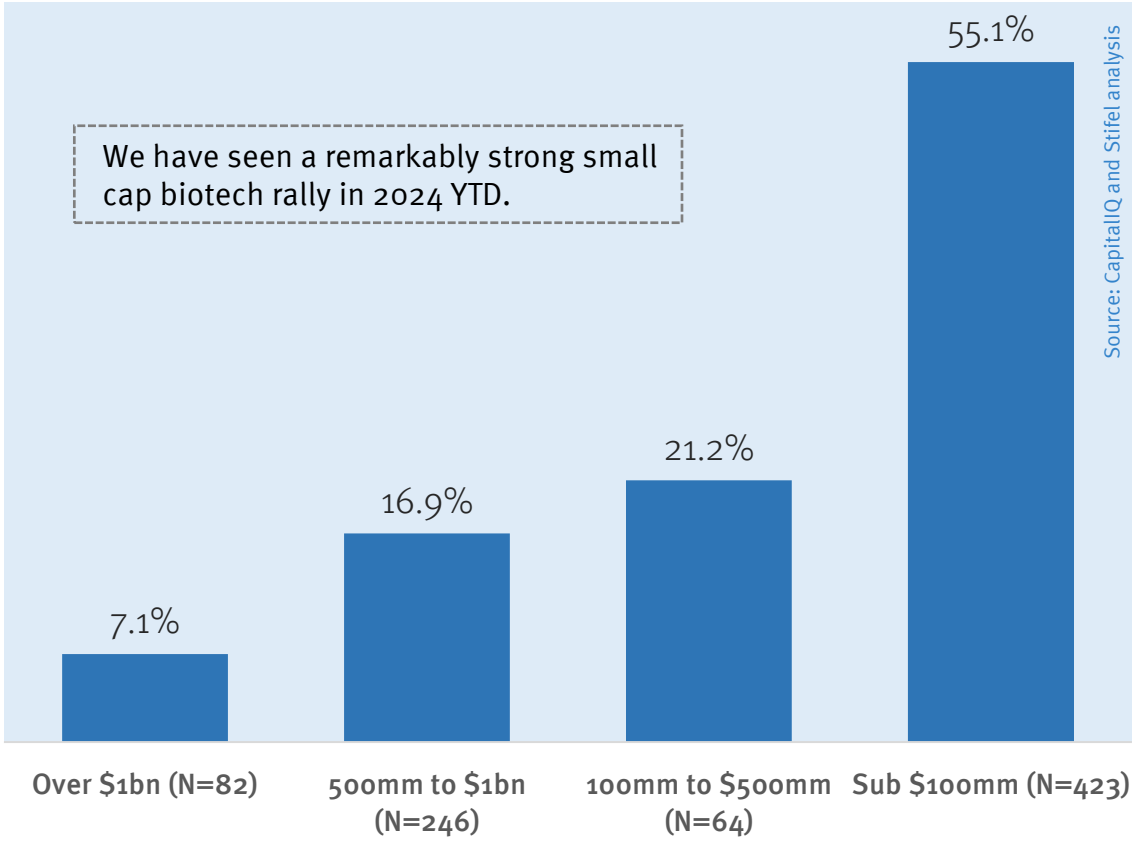


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

It's Been a Great Year for Small Cap Biotech But All of the Rally Happened in Q1 of This Year

Change in Global Biotech Valuations, Dec 31, 2023 to May 10, 2024

(Percent Change in Value of Company Group, N=815)



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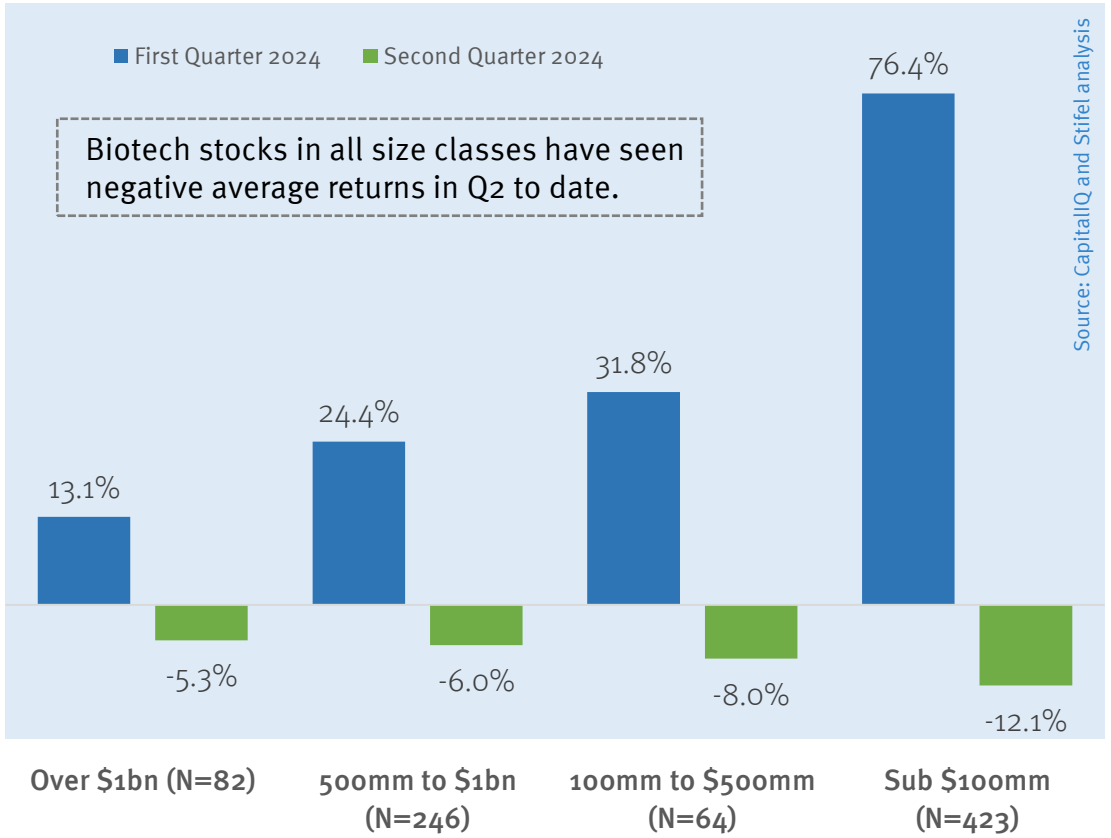
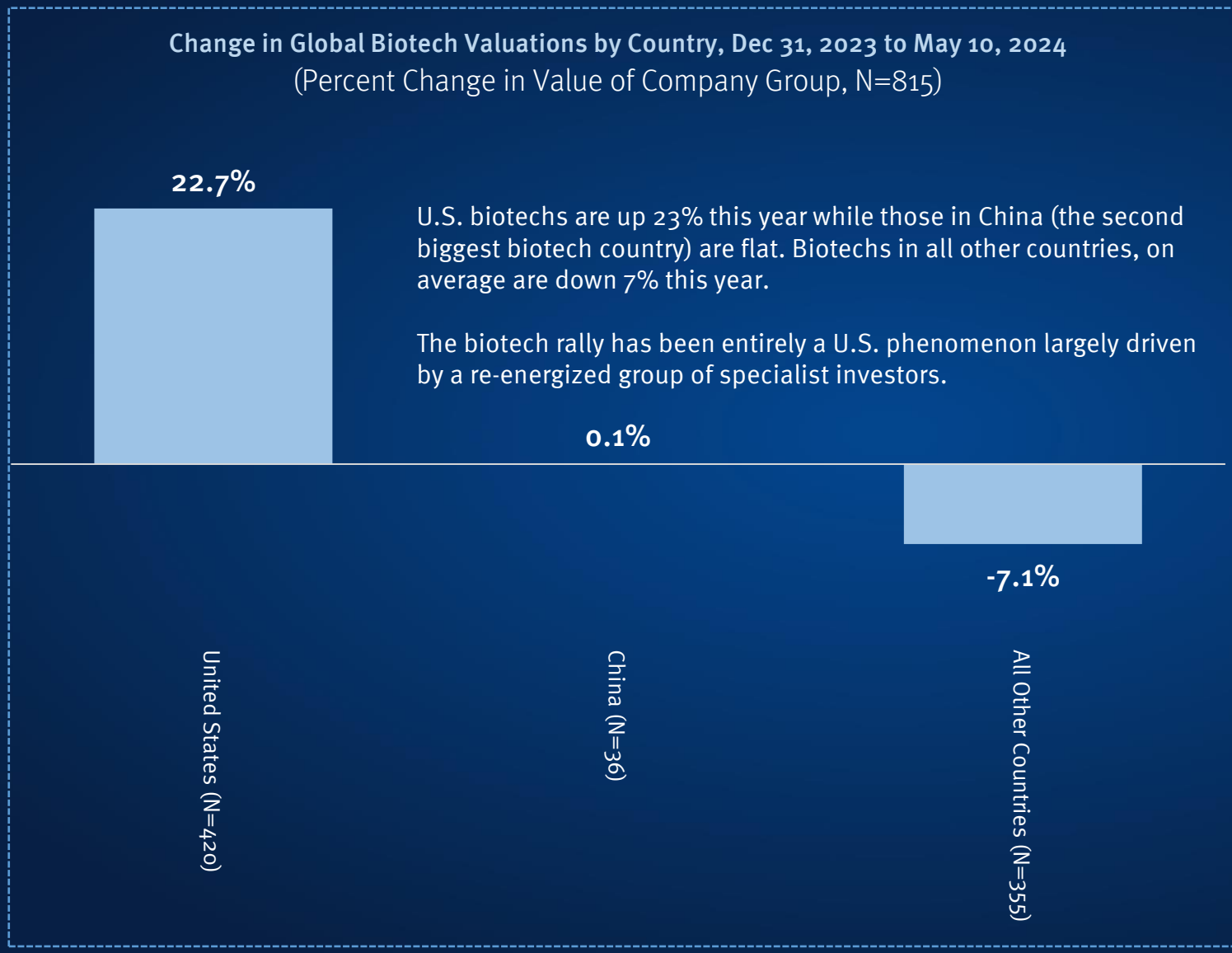


Biotech Rally This Year Strongest in the United States

Change in Global Biotech Valuations by Country, Dec 31, 2023 to May 10, 2024
(Percent Change in Value of Company Group, N=815)



U.S. biotechs are up 23% this year while those in China (the second biggest biotech country) are flat. Biotechs in all other countries, on average are down 7% this year.

The biotech rally has been entirely a U.S. phenomenon largely driven by a re-energized group of specialist investors.

Source: CapitalIQ and Stifel analysis

Life Sciences Sector Total Value Up 1% Last Week

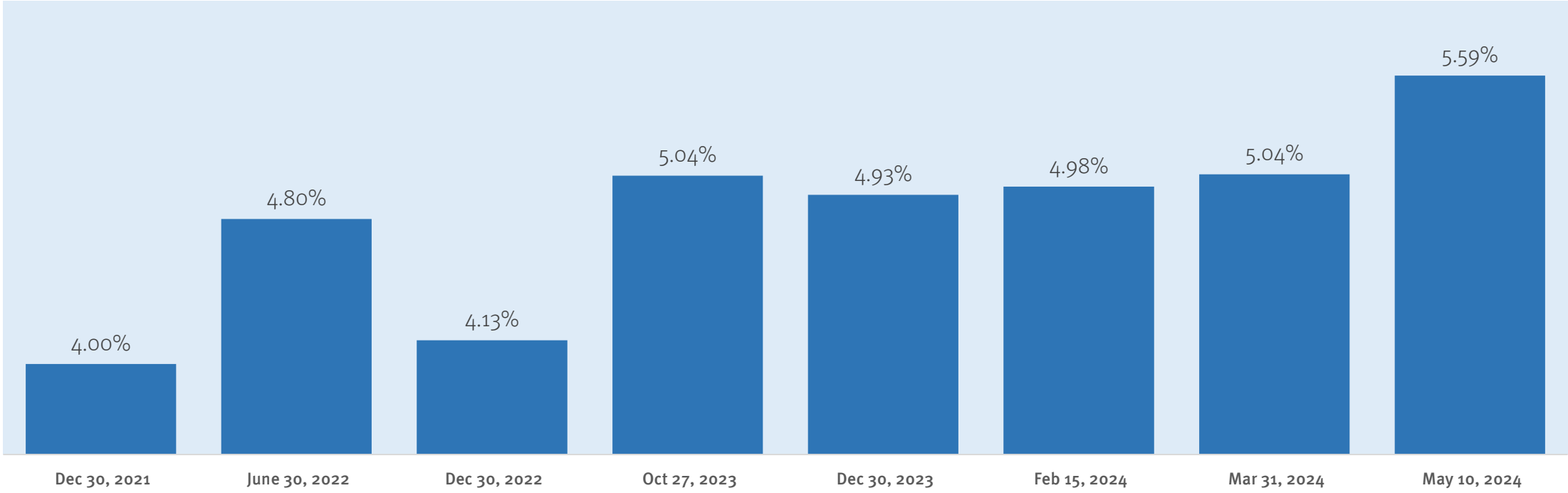
Performance was mixed across the life sciences sector last week as biotech and HCIT dropped while commercial pharma, tools and pharma services gained, on average.

Sector	Firm Count	Enterprise Value (May 10, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$84,122	0.7%	6.7%	8.1%
Biotech	793	$254,393	-5.7%	-7.2%	-5.1%
CDMO	39	$146,995	0.9%	-0.1%	-17.3%
Diagnostics	81	$264,937	0.5%	-3.1%	-2.9%
OTC	30	$27,439	-0.1%	1.6%	-6.8%
Commercial Pharma	716	$6,266,884	1.3%	3.2%	6.6%
Pharma Services	38	$189,137	1.9%	-1.6%	-1.7%
Tools	51	$716,786	3.1%	0.7%	4.0%
Devices	181	$1,675,913	0.2%	-0.6%	-2.0%
HCIT	10	$17,434	-4.7%	-5.0%	-29.5%
Total	**2020**	**$9,635,039**	**1.0%**	**1.7%**	**4.2%**

Source: CapitalIQ and Stifel analysis

Short Interest of Life Sciences Companies at a High Point

Average Short Interest of Global Life Sciences Companies, Dec 2021 to May 2024

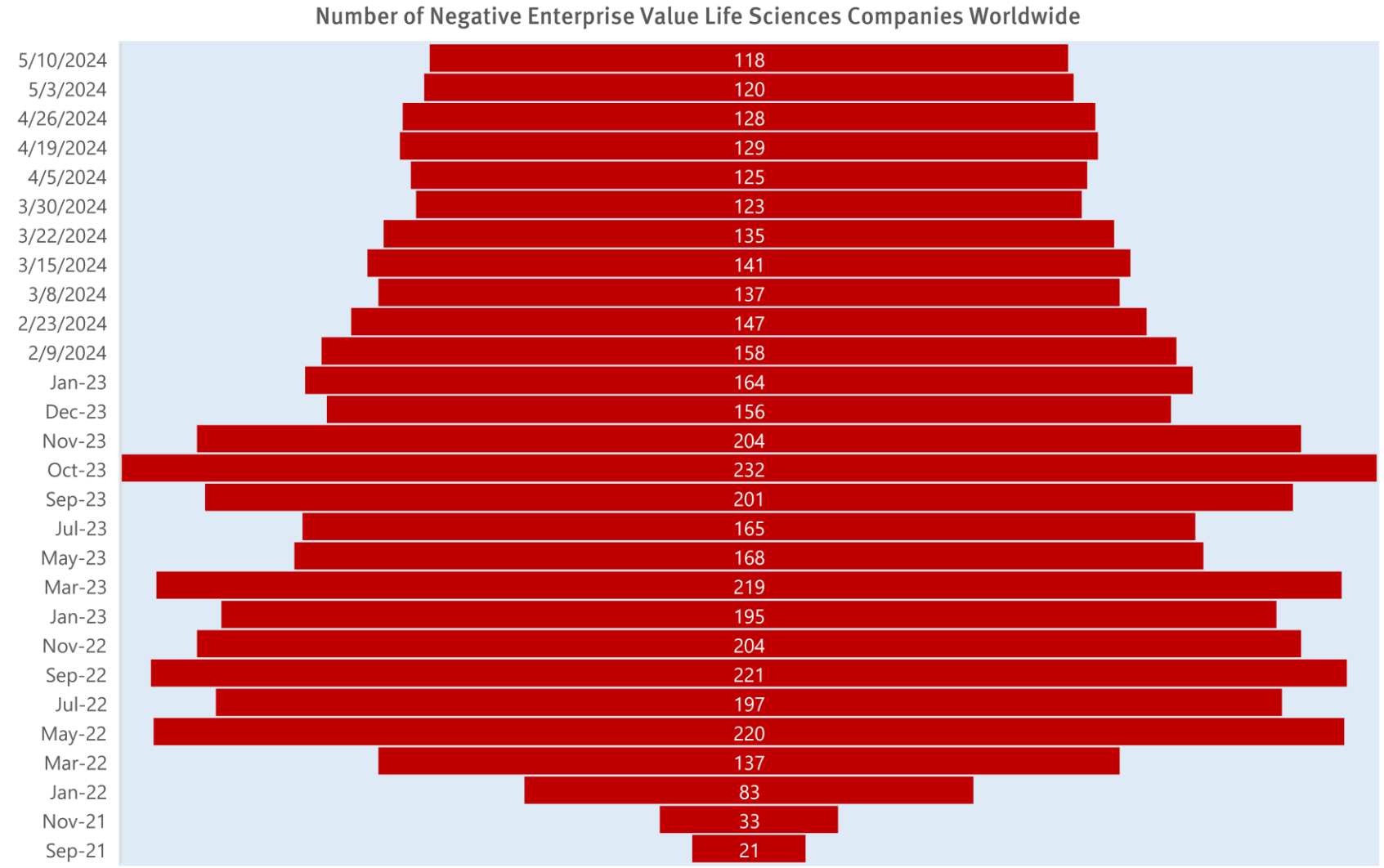


Top Five Shorted Stocks at Time

Dec 30, 2021	June 30, 2022	Dec 30, 2022	Oct 27, 2023	Dec 30, 2023	Feb 15, 2024	Mar 31, 2024	May 10, 2024
Heron	Heron	Editas	Novavax	Novavax	TransCode	Novavax	Biomea
Cassava Sciences	Cassava Sciences	Novavax	Cassava	Biomea	Novavax	Biomea	Novavax
Quince Therap	PMV	Heron	Twist	Cassava	Cassava	Cassava	Cassava
Ocugen	Ocugen	Bluebird	TG Therap	TG Therap	Biomea	Anavex	Altimmune
G1 Therapeutics	bluebird	Allogene	BioCryst	Twist	Coherus	ProKidney	TG Therap

Source: CapitalIQ and Stifel analysis

Number of Negative Enterprise Value Life Sciences Companies Dropped Last Week



The population of negative EV companies continues to shrink.

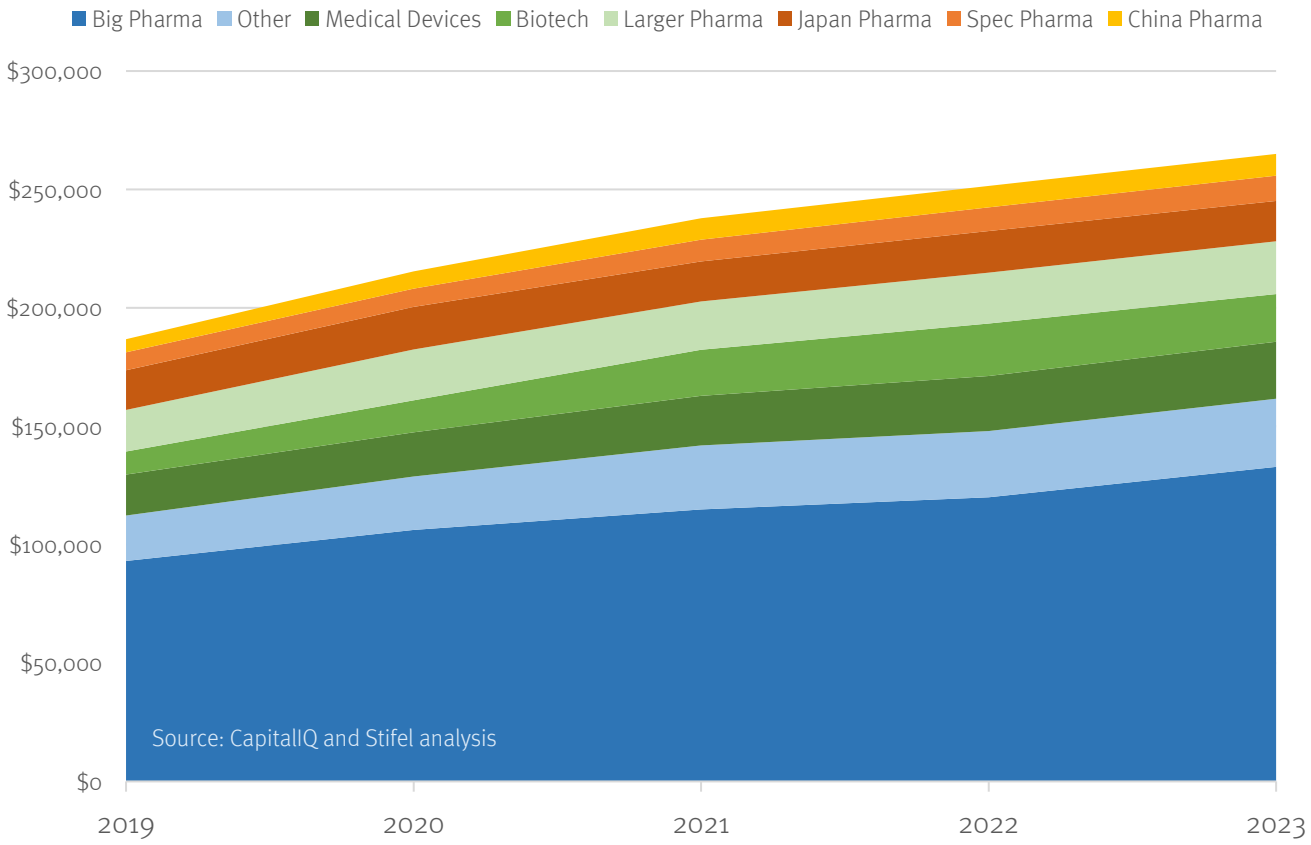
We have encountered several investors who have generated strong returns by buying these companies as market conditions have improved.

Source: CapitalIQ

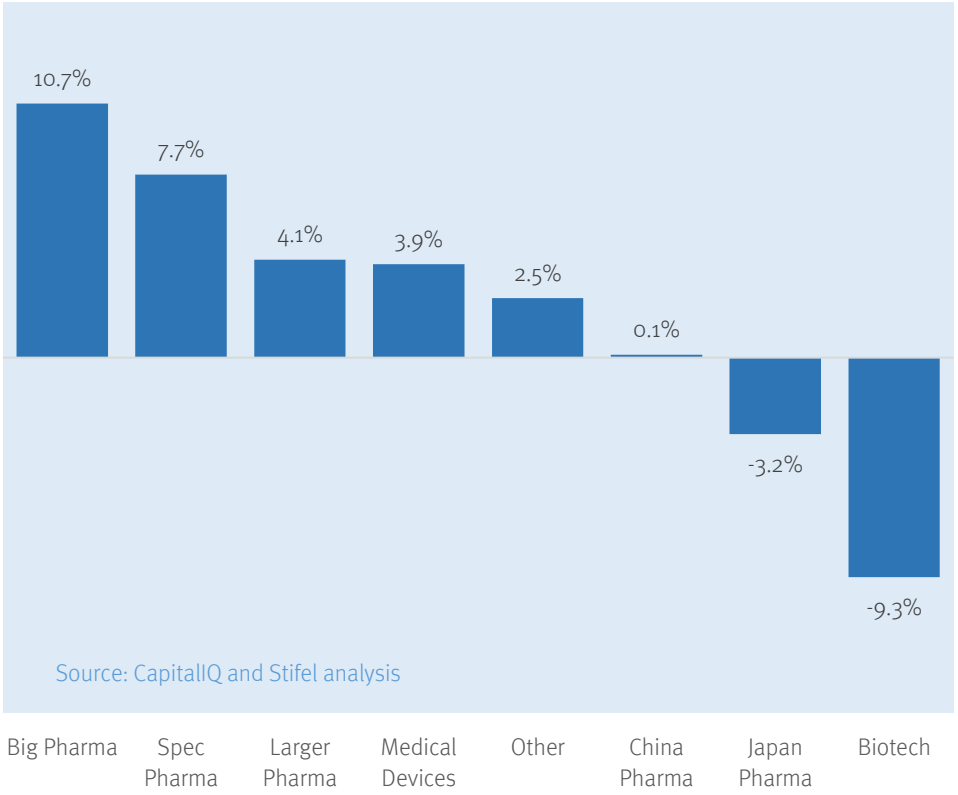
Life Sciences R&D Spend by Subsector: 2023 vs 2022

With 2023 financials now fully reported it's possible to look at what happened to R&D spend in 2023. It did well in big pharma and dropped in biotech and Japan. It seems obvious that the capital drought in biotech took its toll on innovation. The downturn in Japan follows several years of mandatory government price cuts have taken a toll on innovation. One can't help but wonder what R&D spend is going to look like for global pharmas in the years ahead as the impact of the IRA is felt on pharma pocketbooks.

Aggregate R&D Spend in the Life Sciences Sector ($mm), 2019 to 2023



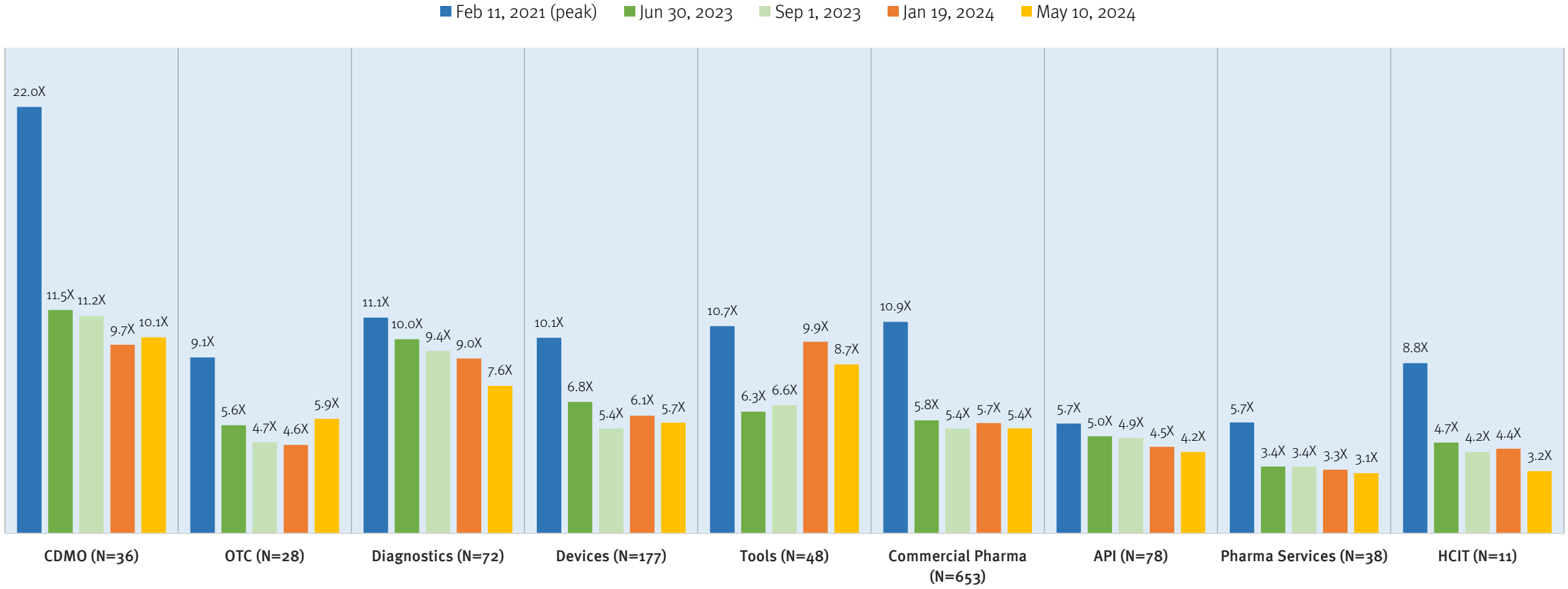
Percent Change in Aggregate Life Sciences Sector R&D Spend by Subsector (2023 vs 2022)



Life Sciences Subsector Revenue Multiples Down in 2024

Revenue Multiples in HCIT, diagnostics, API and pharma services have steadily dropped over the last three years. In contrast, we have seen a recovery in revenue multiples in the CDMO sector. Commercial pharma revenue multiples have been steady for several years.

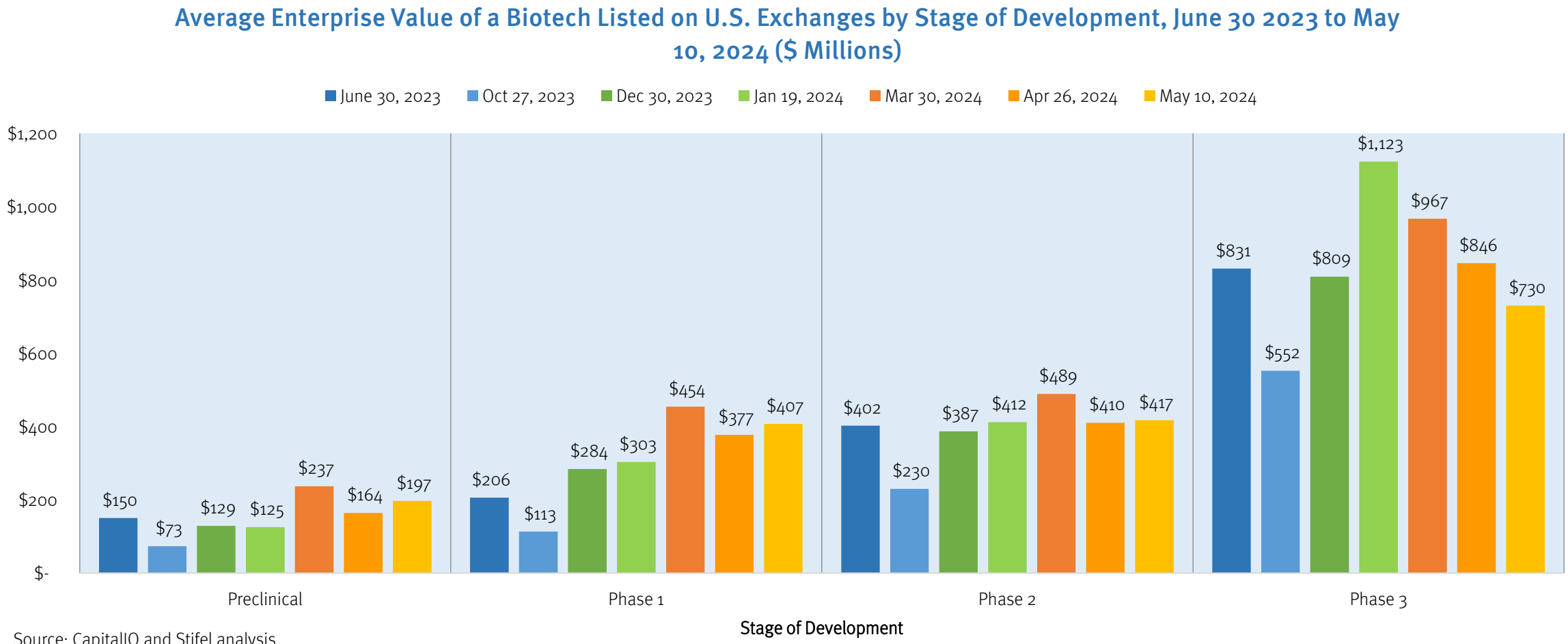
Average Revenue Multiples (EV / Revenue) by Subsector of the Global Life Sciences Sector, Feb 2021 to May 2024



Source: CapitalIQ and Stifel analysis. Revenue multiple is computed as enterprise value on date of interested divided by trailing 12 months revenue. Companies with a multiple of 100X or more or 0.3X or less are trimmed to reduce the effect of extreme outliers.

Premium for Late Stage Biotechs is Dropping

We are seeing investors become much more interested in early and mid-stage biotech stories. There is less investor herding into late-stage companies. Thus, late stage biotechs like Cytokinetics and Rocket have seen their shares decline in the last month. We note that many of the Phase 3 companies identified in the past with “very good” datasets have been acquired. Thus, there may be some negative survivor bias at play here as well.

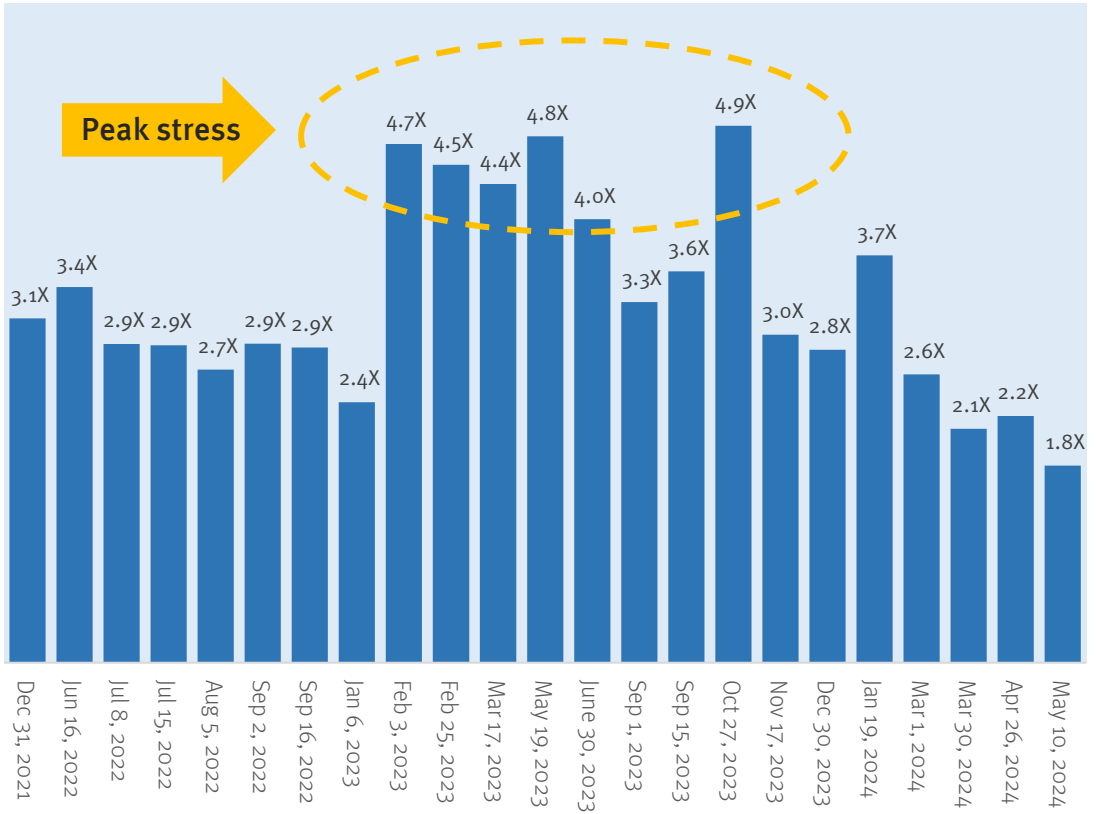


Source: CapitalIQ and Stifel analysis.

Ratio of Average Enterprise Value of a Phase 3 Biotech to Early Stage Dropping

Ratio of Average Value of a U.S. Phase 3 to a Preclinical Stage Biotech, 2021 to 2024

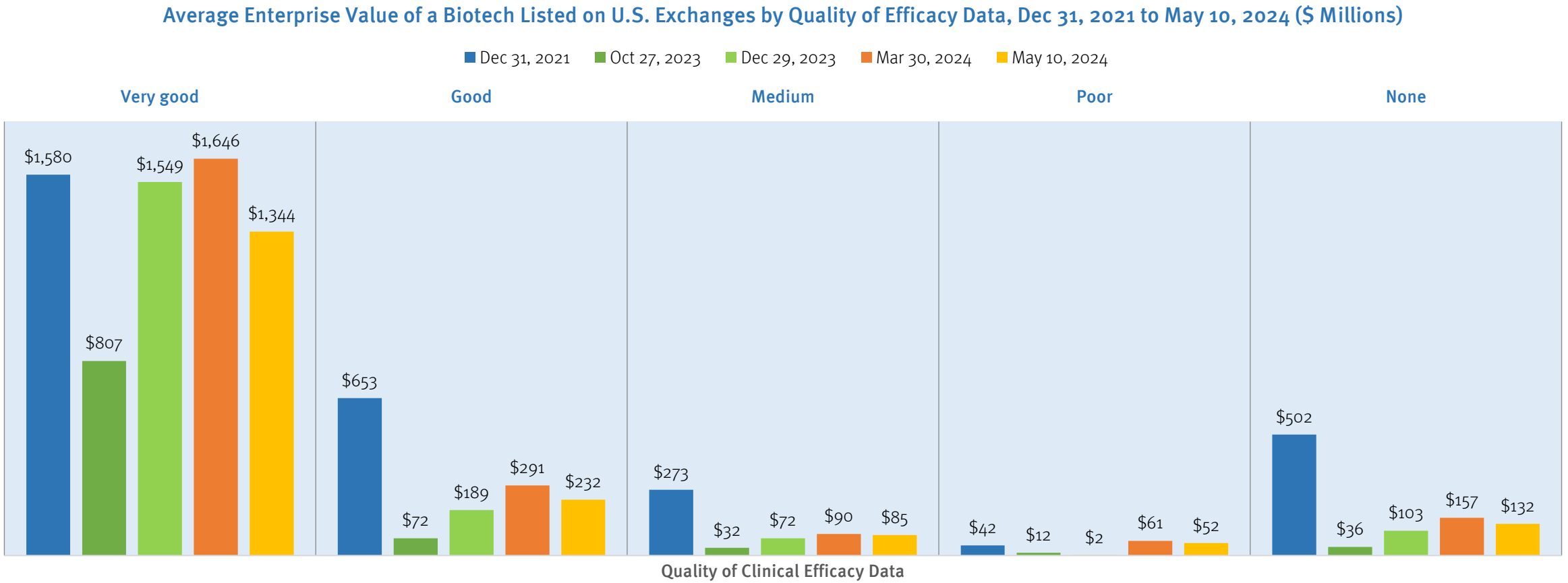
Ratio of Average Value of a U.S. Phase 3 to a Phase 1 Stage Biotech, 2021 to 2024



Source: CapitalIQ and Stifel analysis. Stage of development is measured by last *completed* stage of development.

Data Quality Premium is Also Dropping

While biotechs with very good datasets continue to trade well above those with “good” or “medium” quality datasets, the differential between the two is dropping. Players in the market are coming out of their foxholes and are willing to bet on riskier datasets. We view this as an important sign of market normalization. One way of thinking about this is that specialist investors are increasingly taking an offensive rather than a defensive strategy to stock selection in today’s biotech market. The blazing PIPE market has helped to facilitate this transition.

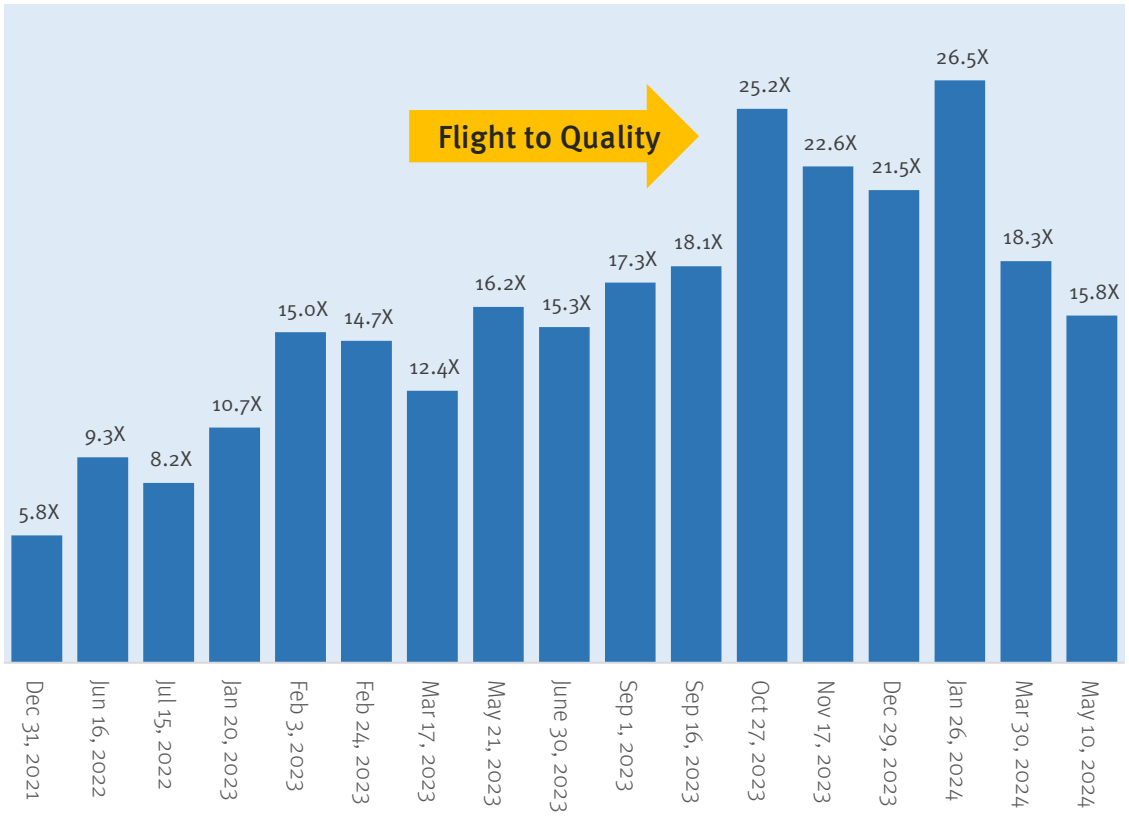


Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company’s lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

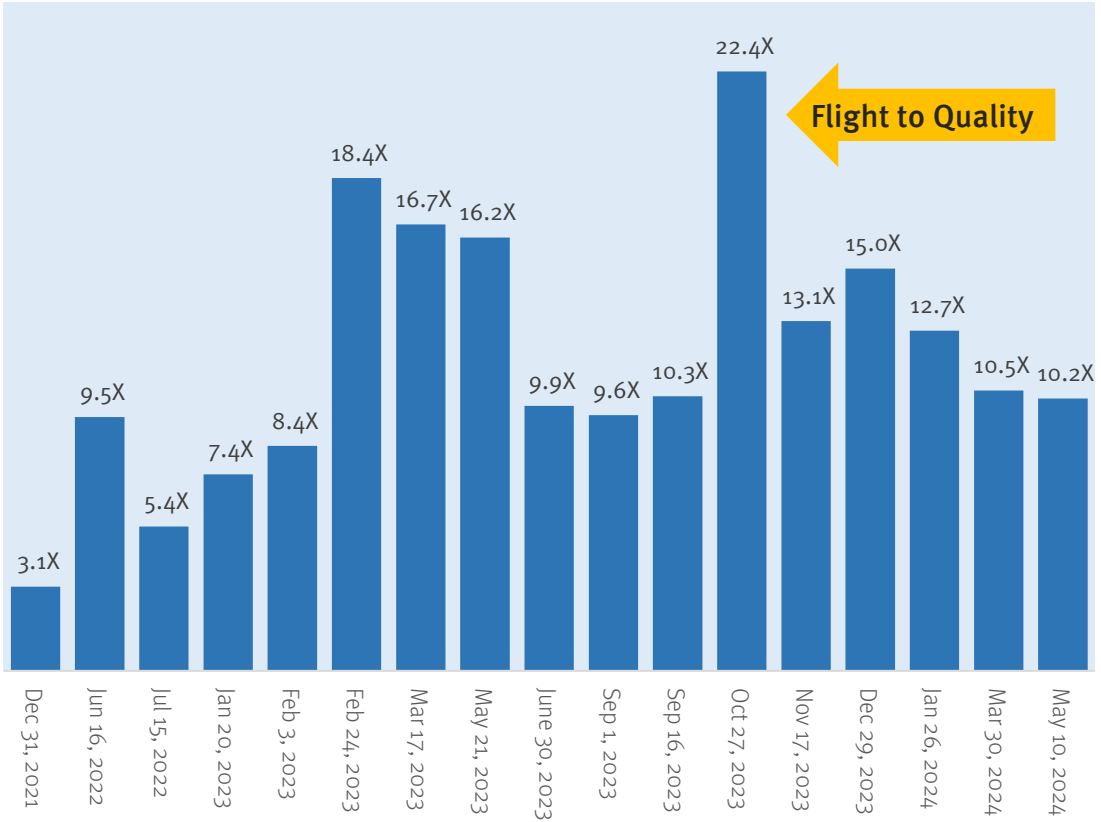
Biotech Quality Premium Gradually Normalizing

Biotech investors place less premium on great data versus only “ok” data today. But, they have yet to return to the halcyon days of 2021 where they would place a high value on a platform-style company with no data at all.

Ratio of Average Enterprise Value of a U.S. Biotech with a "Very Good" Dataset to one with a "Medium" Dataset, 2021 to 2024



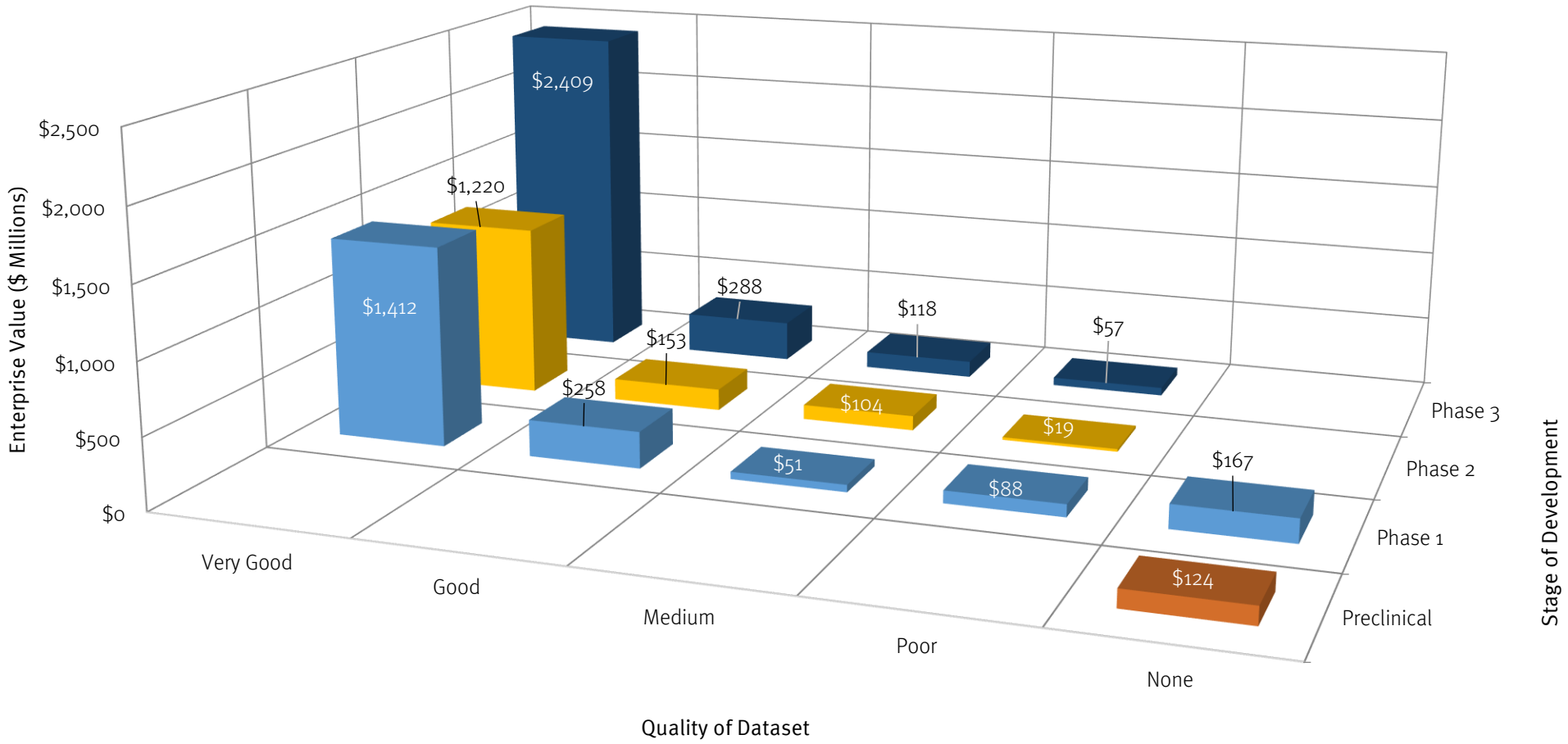
Ratio of Average Enterprise Value of a U.S. Biotech with a Very Good Dataset to one with no data, 2021 to 2024



Source: CapitalIQ and Stifel analysis.

Biotechs With Very Good Phase 3 Data Trade at $2.4 Billion in Value – 12 Times Those with No Data

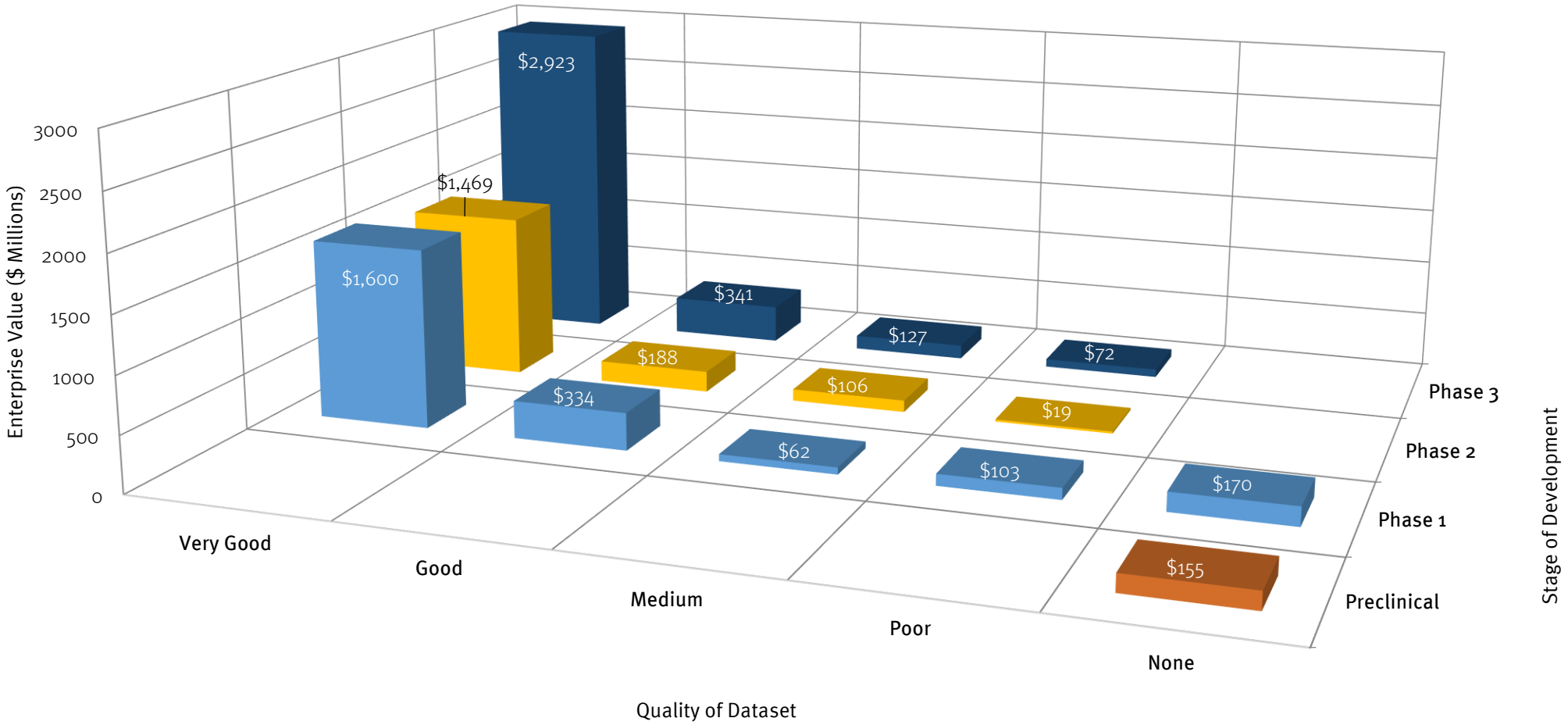
Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, May 10, 2024 ($ millions)



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

For Comparison - Quality x Stage Value Matrix, End of Q1 2024: The Ratio of Biotechs with Very Good Phase 3 Data to No Data Was 15X (vs 12X Today)

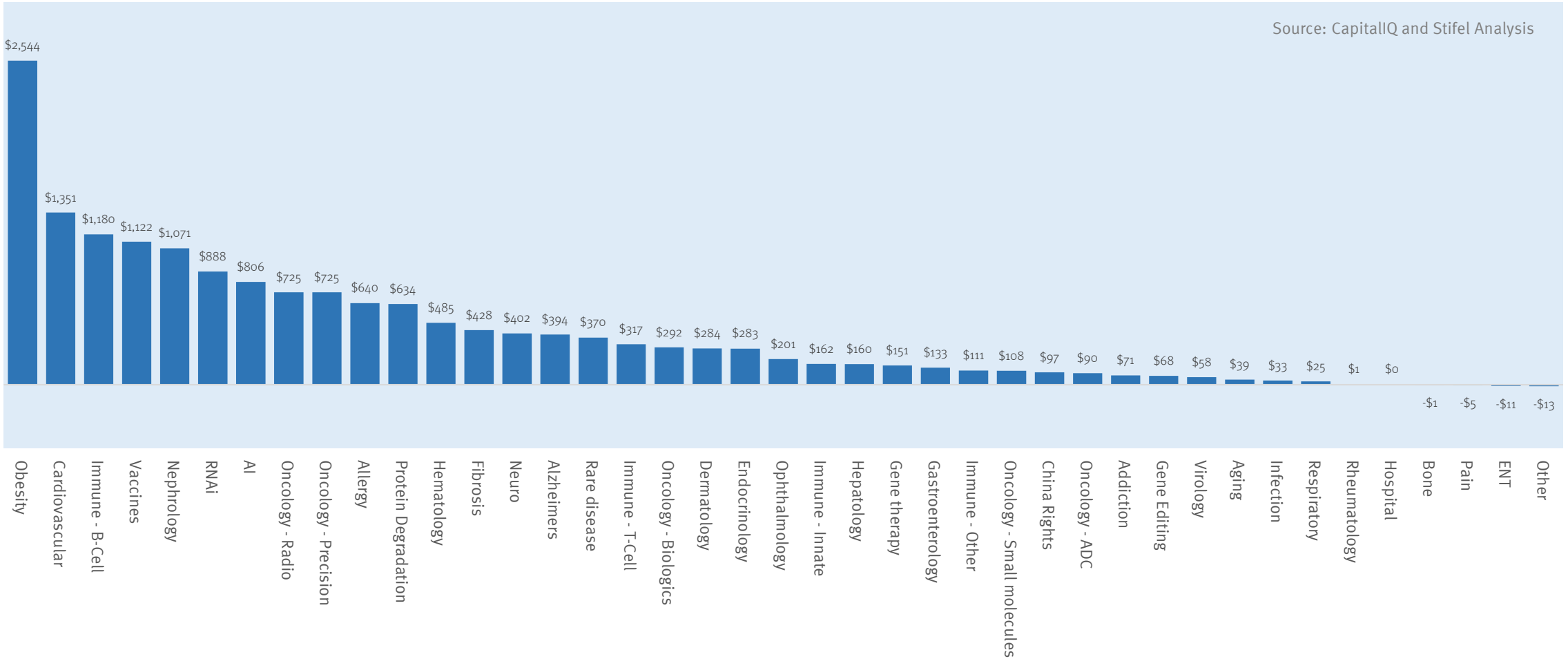
Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data
March 28, 2024 ($ millions)



Source: CapitalIQ and Stifel analysis.

The Most Valued Biotech Fields Today are Obesity, CV, b-Cell, Vaccines, Nephrology, RNAi, AI and Radiopharma

Average Enterprise Value by Subfield of U.S. Biotech, May 10, 2024 ($mm)



Q2 2024 Has Seen Value Drops in the Hottest Areas like Obesity, B-Cell and CV. Radiopharma and T-Cell Immunity Stories Gained Value

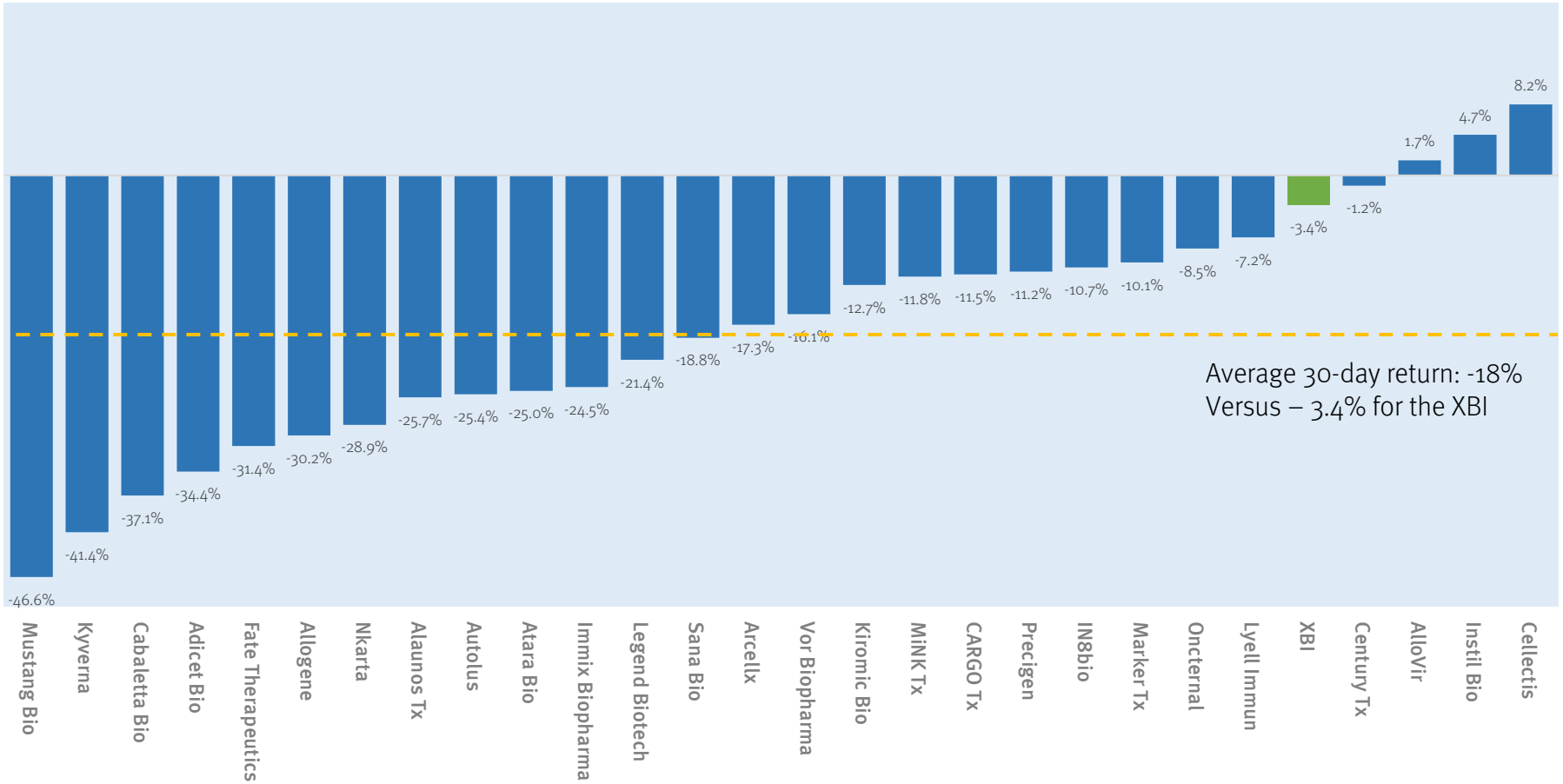
Average Enterprise Value by Field of Biotech, U.S. Domiciled Companies, 2020 to 2024, $mm

Field	Company Count	Dec 29, 2020	Dec 31, 2021	Dec 31, 2022	Jun 30, 2023	Dec 30, 2023	Mar 30, 2024	May 10, 2024	Change (Mar 30, '24 to May 10, '24)	Change (Dec 30, '23 to May 10, '24)	Change (Dec 30, '21 to May 10, '24)
Obesity	4	$78	$72	$284	$1,417	$1,121	$2,951	$2,544	-13.8%	126.9%	3436.8%
Cardiovascular	8	$443	$911	$1,643	$1,366	$2,016	$2,027	$1,351	-33.3%	-33.0%	48.2%
Immune - B-Cell	4	$1,077	$198	$741	$830	$1,898	$1,537	$1,180	-23.2%	-37.8%	497.0%
Vaccines	6	$442	$541	$609	$671	$904	$1,289	$1,122	-13.0%	24.1%	107.4%
Nephrology	7	$49	$157	$297	$508	$407	$867	$1,071	23.5%	163.0%	582.7%
RNAi	4	$344	$235	$362	$168	$209	$965	$888	-8.0%	325.8%	278.3%
Artificial Intelligence	3	$0	$1,632	$377	$412	$823	$948	$806	-15.0%	-2.1%	-50.6%
Precision Oncology	27	$892	$689	$394	$476	$648	$745	$725	-2.7%	11.9%	5.2%
Radiopharma	4	$30	$35	$61	$50	$185	$621	$725	16.7%	291.9%	1943.6%
Allergy	4	$1,950	$423	$675	$566	$617	$708	$640	-9.6%	3.7%	51.1%
Protein Degradation	4	$1,179	$1,326	$263	$260	$388	$770	$634	-17.7%	63.4%	-52.2%
Hematology	5	$764	$325	$448	$310	$376	$584	$485	-17.0%	29.0%	49.3%
Fibrosis	5	$671	$452	$281	$592	$504	$538	$428	-20.4%	-15.1%	-5.2%
Neuro	38	$477	$417	$338	$395	$400	$456	$402	-11.8%	0.5%	-3.5%
Alzheimers	7	$1,409	$1,280	$1,010	$1,020	$528	$655	$394	-39.8%	-25.4%	-69.2%
Rare disease	35	$1,498	$1,269	$497	$497	$387	$495	$369	-25.5%	-4.7%	-70.9%
Immune - T-Cell	7	$716	$140	$59	$314	$188	$288	$317	10.1%	68.6%	127.0%
Oncology - Biologics	72	$689	$501	$180	$165	$171	$366	$292	-20.2%	70.8%	-41.7%
Dermatology	5	$362	$141	$52	$101	$146	$281	$284	1.1%	94.5%	101.4%
Endocrinology	11	$143	$191	$83	$62	$171	$293	$283	-3.4%	65.1%	48.2%
Ophthalmology	14	$995	$503	$138	$208	$152	$373	$201	-46.1%	32.2%	-60.0%
Immune - Innate	7	$111	$507	$468	$397	$37	$209	$162	-22.5%	337.8%	-68.1%
Hepatology	10	$481	$291	$458	$466	$175	$250	$160	-36.0%	-8.6%	-45.0%
Gene therapy	2	$249	$473	$147	$213	$235	$174	$151	-13.2%	-35.7%	-68.1%
Gastroenterology	2	$990	$393	$265	$338	$116	$106	$133	25.5%	15.1%	-66.1%
Immune - Other	6	$143	$169	$20	$36	$38	$157	$111	-29.3%	192.1%	-34.4%
Oncology - Small molecules	43	$394	$279	$57	$122	$107	$151	$108	-28.5%	0.9%	-61.2%
China Focused	2	$0	$475	$111	$97	$201	$248	$97	-60.9%	-51.8%	-79.6%
Oncology - ADC	4	$698	$319	$121	$22	-$9	$146	$90	-38.4%	-1100.0%	-71.8%
Gene Editing	4	$107	$572	$200	$131	$309	$312	$68	-78.2%	-78.0%	-88.1%
Virology	12	$1,020	$582	$90	$99	$17	$76	$58	-23.7%	235.8%	-90.0%
Aging	3	$90	$113	$23	$42	$16	$61	$39	-36.1%	143.8%	-65.4%
Infection	7	$165	$145	$35	$29	$40	$56	$33	-41.1%	-17.5%	-77.2%
Hospital	1	$1	$11	$5	$6	$10	$4	$0	-90.0%	-95.8%	-96.2%
Pain	2	$143	$55	-$13	-$5	-$6	-$3	-$5	66.7%	-21.7%	-109.0%
ENT	2	$34	$15	-$3	$62	$92	$151	-$11	-107.3%	-112.0%	-173.3%

Source: CapitalIQ and Stifel analysis.

A Tough Month for Cell Therapy Biotechs Focused on B-Cell Autoimmunity and Oncology

Share Price Return of US and European Public CAR-t and NK Cell Therapy Companies in Autoimmune and Oncology, Apr 11 to May 10, 2024



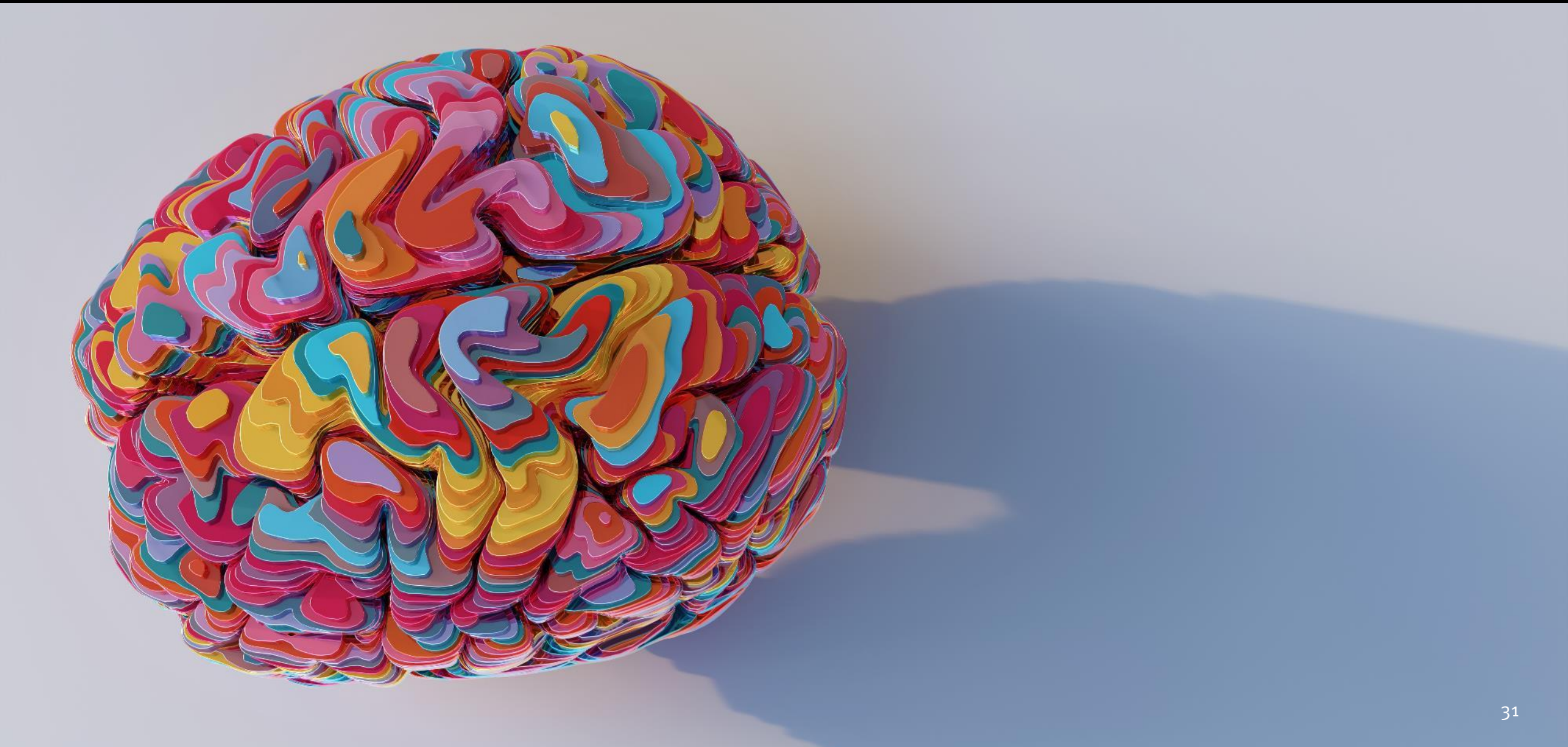
We have communicated with investors and management teams in the last week to understand what is going on with **cell therapy** in biotech.

Investors have cooled, in general, on complex therapeutics in oncology and immunology such as CAR-t, NK's, TCR's and, even, oncolytic viruses. They increasingly favor ADCs, antibodies and engagers.

The thinking is that while engagers can't quite get the full benefit of a CAR-t, they are far less expensive and don't involve lengthy vein-to-vein times. Investors have noted slow uptake of CAR-t's commercially, slow enrollment of studies in autoimmunity and cancer and difficulty in the supply chain.

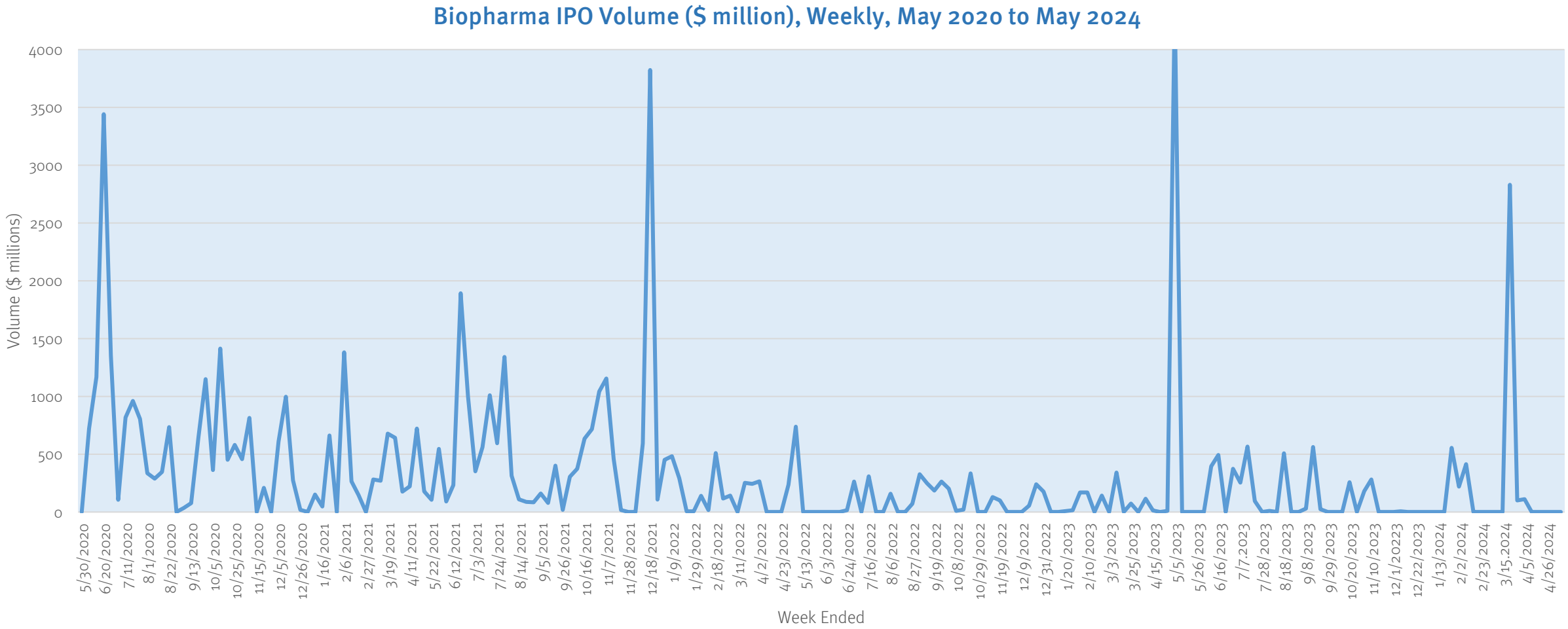
Management teams, in contrast, note that CAR-t can *eliminate* pathologic B-cells with far more profound benefit for patients and can avoid the chronic use of antibodies, engagers and the like. Our own view is that there will be room for both types of therapies.

Capital Markets Update



No IPO Activity Last Week

The IPO market remained inactive last week. The last company to go public in the U.S. or Europe debuted five weeks ago. The pipeline of IPO's on file has continued to swell as issuers anticipate an opening of the window after Memorial Day.



Source: Data from CapitalIQ and Stifel research.

Pharma Services Powerhouse Indegene IPO Heavily Oversubscribed in India Last Week

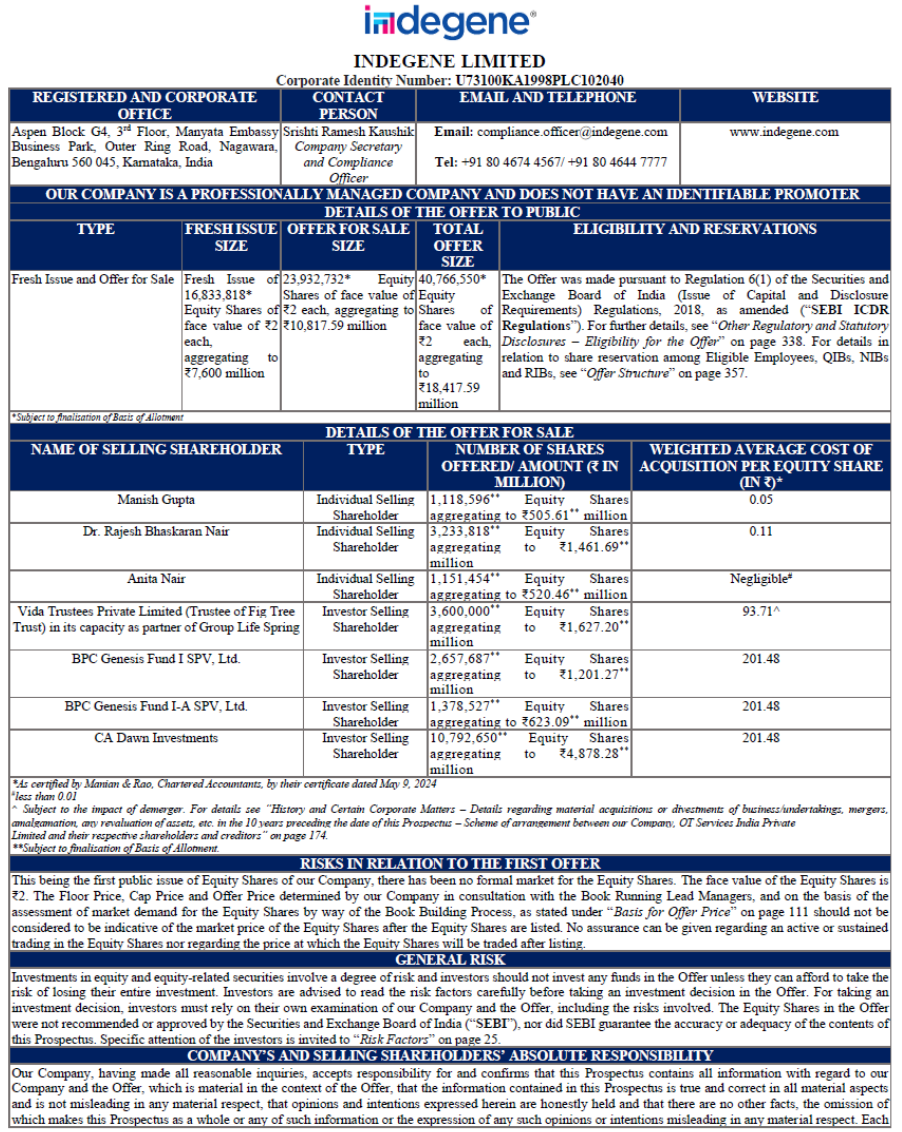
MoneyControl, May 10, 2024 (Excerpt)

The Indegene stock is expected to make a decent debut on the bourses on May 13. Analysts expect the shares to list at a 40-65 percent premium over the IPO price, somewhere between Rs 700 and Rs 760.

Ahead of the listing, the shares were commanding a 61 percent premium in the grey market, an unofficial ecosystem where shares start trading before the allotment in the IPO and continue till the listing day. Most investors track the grey market premium (GMP) to get an idea of the listing price.

“Considering the strong subscription demand on the last day of the issue with QIB demand raised to 192x gives good room for healthy listing gain in the range of 40-50 percent and even above against the issue price,” said Prashanth Tapse, Research Analyst, Sr VP Research at Mehta Equities.

The issue was subscribed 69.91 times as investors bought 201.81 crore equity shares against the 2.88 crore shares on offer between May 6 and May 8. Non-institutional investors (high net worth individuals) were at the forefront, picking 55.07 times the reserved portion, followed by qualified institutional buyers or QIBs who bought 197.55 times the part set aside for them. The retail investor portion was booked 7.95 times.



indegene

INDEGENE LIMITED

Corporate Identity Number: U73100KA1998PLC102040

REGISTERED AND CORPORATE OFFICE	CONTACT PERSON	EMAIL AND TELEPHONE	WEBSITE
Aspen Block G4, 3rd Floor, Manyata Embassy Business Park, Outer Ring Road, Nagawara, Bengaluru 560 045, Karnataka, India	Srishti Ramesh Kaushik *Company Secretary and Compliance Officer*	**Email:** compliance.officer@indegene.com **Tel:** +91 80 4674 4567/ +91 80 4644 7777	www.indegene.com

OUR COMPANY IS A PROFESSIONALLY MANAGED COMPANY AND DOES NOT HAVE AN IDENTIFIABLE PROMOTER

DETAILS OF THE OFFER TO PUBLIC

TYPE	FRESH ISSUE SIZE	OFFER FOR SALE SIZE	TOTAL OFFER SIZE	ELIGIBILITY AND RESERVATIONS
Fresh Issue and Offer for Sale	Fresh Issue of 16,833,818* Equity Shares of face value of ₹2 each, aggregating to ₹7,600 million	23,932,732* Equity Shares of face value of ₹2 each, aggregating to ₹10,817.59 million	40,766,550* Equity Shares of face value of ₹2 each, aggregating to ₹18,417.59 million	The Offer was made pursuant to Regulation 6(1) of the Securities and Exchange Board of India (Issue of Capital and Disclosure Requirements) Regulations, 2018, as amended ("**SEBI ICDR Regulations**"). For further details, see "*Other Regulatory and Statutory Disclosures – Eligibility for the Offer*" on page 338. For details in relation to share reservation among Eligible Employees, QIBs, NIBs and RIBs, see "*Offer Structure*" on page 357.

**Subject to finalization of Basis of Allotment*

DETAILS OF THE OFFER FOR SALE

NAME OF SELLING SHAREHOLDER	TYPE	NUMBER OF SHARES OFFERED/ AMOUNT (₹ IN MILLION)	WEIGHTED AVERAGE COST OF ACQUISITION PER EQUITY SHARE (IN ₹)*
Manish Gupta	Individual Selling Shareholder	1,118,596** Equity Shares aggregating to ₹505.61** million	0.05
Dr. Rajesh Bhaskaran Nair	Individual Selling Shareholder	3,233,818** Equity Shares aggregating to ₹1,461.69** million	0.11
Anita Nair	Individual Selling Shareholder	1,151,454** Equity Shares aggregating to ₹520.46** million	Negligible#
Vida Trustees Private Limited (Trustee of Fig Tree Trust) in its capacity as partner of Group Life Spring	Investor Selling Shareholder	3,600,000** Equity Shares aggregating to ₹1,627.20** million	93.71^
BPC Genesis Fund I SPV, Ltd.	Investor Selling Shareholder	2,657,687** Equity Shares aggregating to ₹1,201.27** million	201.48
BPC Genesis Fund I-A SPV, Ltd.	Investor Selling Shareholder	1,378,527** Equity Shares aggregating to ₹623.09** million	201.48
CA Dawn Investments	Investor Selling Shareholder	10,792,650** Equity Shares aggregating to ₹4,878.28** million	201.48

**As certified by Manian & Rao, Chartered Accountants, by their certificate dated May 9, 2024*
#less than 0.01
^ Subject to the impact of demerger. For details see "History and Certain Corporate Matters – Details regarding material acquisitions or divestments of business/undertakings, mergers, amalgamation, any revaluation of assets, etc. in the 10 years preceding the date of this Prospectus – Scheme of arrangement between our Company, OT Services India Private Limited and their respective shareholders and creditors" on page 174.
***Subject to finalisation of Basis of Allotment.*

RISKS IN RELATION TO THE FIRST OFFER

This being the first public issue of Equity Shares of our Company, there has been no formal market for the Equity Shares. The face value of the Equity Shares is ₹2. The Floor Price, Cap Price and Offer Price determined by our Company in consultation with the Book Running Lead Managers, and on the basis of the assessment of market demand for the Equity Shares by way of the Book Building Process, as stated under "*Basis for Offer Price*" on page 111 should not be considered to be indicative of the market price of the Equity Shares after the Equity Shares are listed. No assurance can be given regarding an active or sustained trading in the Equity Shares nor regarding the price at which the Equity Shares will be traded after listing.

GENERAL RISK

Investments in equity and equity-related securities involve a degree of risk and investors should not invest any funds in the Offer unless they can afford to take the risk of losing their entire investment. Investors are advised to read the risk factors carefully before taking an investment decision in the Offer. For taking an investment decision, investors must rely on their own examination of our Company and the Offer, including the risks involved. The Equity Shares in the Offer were not recommended or approved by the Securities and Exchange Board of India ("**SEBI**"), nor did SEBI guarantee the accuracy or adequacy of the contents of this Prospectus. Specific attention of the investors is invited to "*Risk Factors*" on page 25.

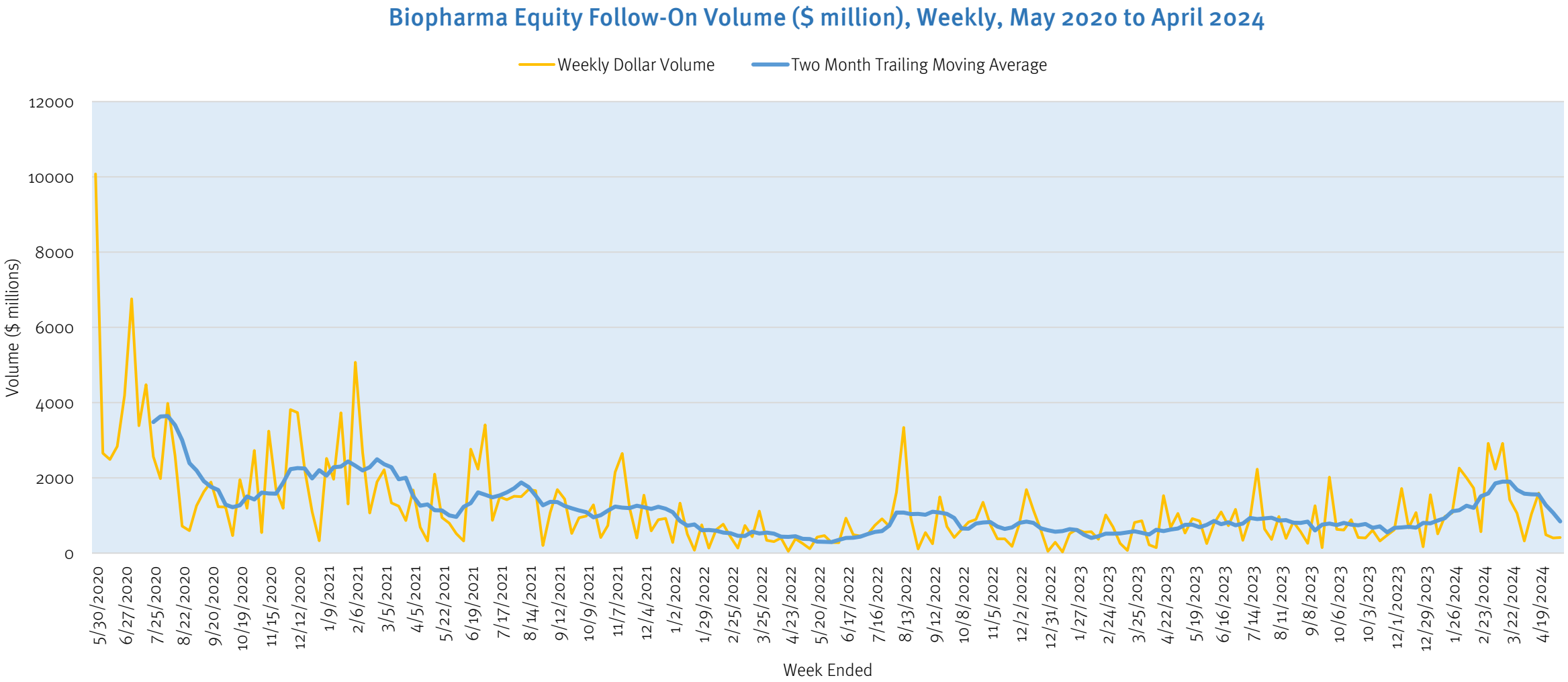
COMPANY'S AND SELLING SHAREHOLDERS' ABSOLUTE RESPONSIBILITY

Our Company, having made all reasonable inquiries, accepts responsibility for and confirms that this Prospectus contains all information with regard to our Company and the Offer, which is material in the context of the Offer, that the information contained in this Prospectus is true and correct in all material aspects and is not misleading in any material respect, that opinions and intentions expressed herein are honestly held and that there are no other facts, the omission of which makes this Prospectus as a whole or any of such information or the expression of any such opinions or intentions misleading in any material respect. Each

Source: https://www.moneycontrol.com/news/business/ipo/indegene-listing-stock-expected-to-list-at-40-65-premium-over-ipo-price-on-may-13-12719532.html

Follow-On Market Quiet Last Week

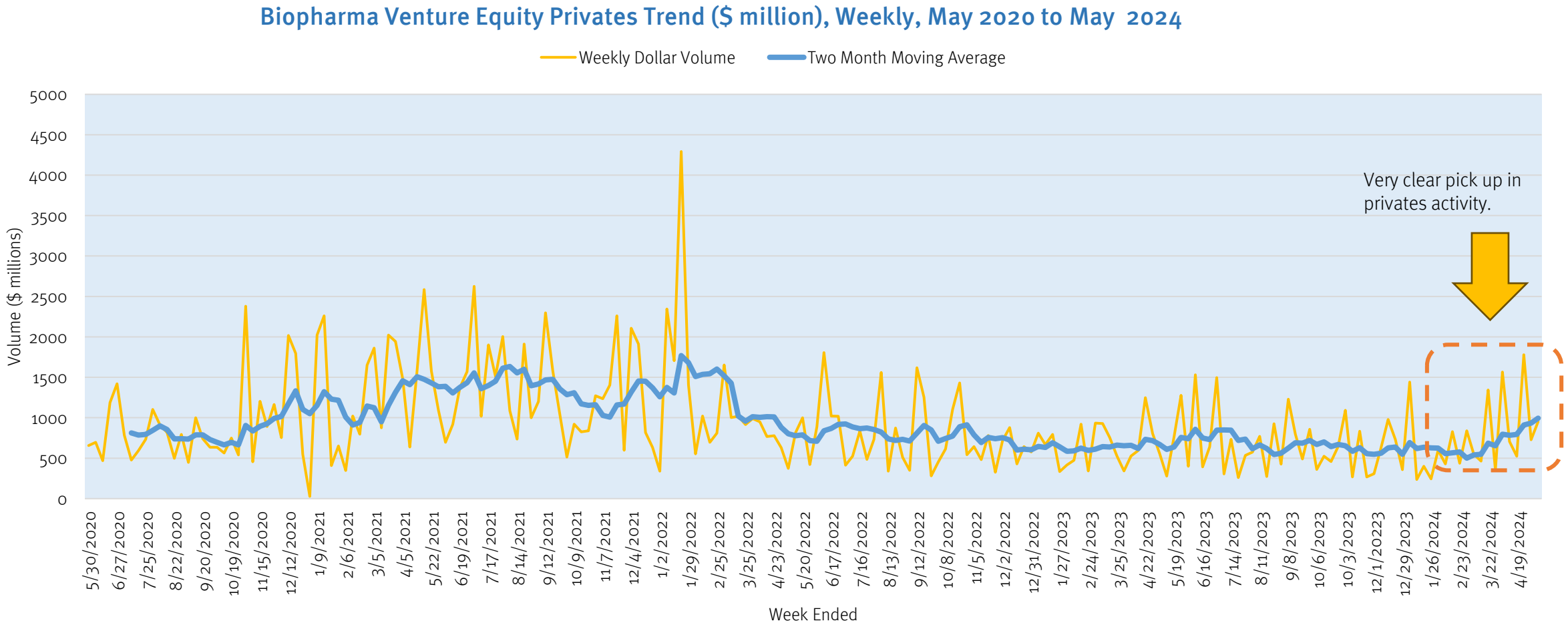
The follow-on market remained quiet last week as the inflation situation sorts itself out. A total of $416 million was raised across 15 issues. The largest issues were by Kelun Biotech ($155mm), ADC Therapeutics ($105mm) and OptiNose ($55mm).



Source: Data from CapitalIQ.

Private Venture Equity Market Active Last Week

The venture private market was active last week with $951 million raised by issuers in this market. The largest issues were Zenas ($200mm), Bluejay ($182mm), Taiyi Guanjia ($127mm), Attovia Therapeutics ($105mm) and Aardvark Therapeutics ($85mm).



Source: Data from CapitalIQ, Crunchbase.

Zenas BioPharma Announces Upsized $200 Million Series C Financing to Advance Immunology-Focused Clinical Development

Waltham, Mass, May 7, 2024: Zenas BioPharma, a global biopharmaceutical company committed to becoming a leader in the development and commercialization of inflammation and immunology-directed therapies, today announced the closing of an upsized $200 million Series C preferred stock financing. The financing round was led by SR One along with NEA, Norwest Venture Partners, and Delos Capital with significant participation from Enavate Sciences and Longitude Capital. Additional new investors, the Federated Hermes Kaufmann Funds, and Arrowmark Partners, along with existing investors, Fairmount, Wellington Management, Rock Springs Capital, Pivotal bioVenture Partners, Vivo Capital, Quan Venture Fund, and Superstring Capital participated in the financing.

In conjunction with the financing, Jake Nunn, venture partner at SR One, and Tim Xiao, Partner at Delos Capital, joined Zenas' Board of Directors.

Proceeds will support ongoing mid- to late-stage clinical development programs for the Company's lead product candidate, obexelimab, a bifunctional monoclonal antibody designed to bind both CD19 and FcγRIIb to inhibit the activity of B cells, plasmablasts, and CD19-expressing plasma cells.

The obexelimab clinical programs include an ongoing Phase 3 registration-directed trial in IgG4-Related Disease, two planned Phase 2 randomized controlled trials in Multiple Sclerosis and Systemic Lupus Erythematosus, and an ongoing open label Phase 2 trial in Warm Autoimmune Hemolytic Anemia.

"We are pleased and appreciative of the support we have received from this group of tremendous life sciences investors as we advance the ongoing obexelimab development program across multiple auto-immune diseases."

Lonnie Moulder
Chief Executive Officer
Zenas

Source: https://zenasbio.com/news/zenas-biopharma-announces-upsized-200-million-series-c-financing-to-advance-mid-and-late-stage-immunology-focused-clinical-development-programs/

Bluejay Therapeutics Secures $182 Million in Series C Financing to Propel Clinical Pipeline

SAN MATEO, Calif. May 9, 2024 - Bluejay Therapeutics, a leader in the development of novel therapeutics, today announced the successful closure of a $182 million Series C financing round. This capital infusion will accelerate the clinical development of BJT-778, as the treatment for chronic hepatitis D (HDV). The funds will also support the progression of additional promising candidates in Bluejay's robust pipeline for the treatment for chronic hepatitis B. As previously announced, BJT-778 has received PRIME designation from EMA based on early results from the Phase 1/2 study in HDV.

This financing round was co-led by Frazier Life Sciences and a life science focused institutional investment firm, with significant contributions from both new and existing investors, including RA Capital Management, T. Rowe Price, Wellington Management, Novo Holdings, RiverVest Venture Partners, Octagon Capital, Arkin Bio Ventures, HBM Healthcare Investments and Unicorn Capital.

Following the completion of the Series C financing, Bluejay is excited to welcome New Board Member, Daniel Estes, a General Partner at Frazier, to its Board of Directors.

Bluejay Therapeutics is a private biopharmaceutical company focused on the development of treatments for viral and liver diseases. The Company's lead program, BJT-778 is a potentially best-in-class fully human IgG1 monoclonal antibody against hepatitis B surface antigen (anti-HBsAg mAb), being developed for both chronic HBV and HDV. BJT-778 is designed to provide anti-HBV and anti-HDV benefits by neutralizing and clearing HBV and HDV virions as well as by depleting HBsAg-containing subviral particles, which may help to reconstitute a subject's antiviral immunity and contribute to functional cure for CHB.

Source: https://www.globenewswire.com/news-release/2024/05/09/2878595/0/en/Bluejay-Therapeutics-Secures-182-Million-in-Series-C-Financing-to-Propel-Clinical-Pipeline.html

"We are immensely grateful for the robust support from both new and returning investors, which reflects confidence in our strategy and our team's ability to deliver on our mission. This funding not only empowers us to drive our lead assets through critical clinical trials but also enhances our capacity to address significant unmet medical needs in global health."

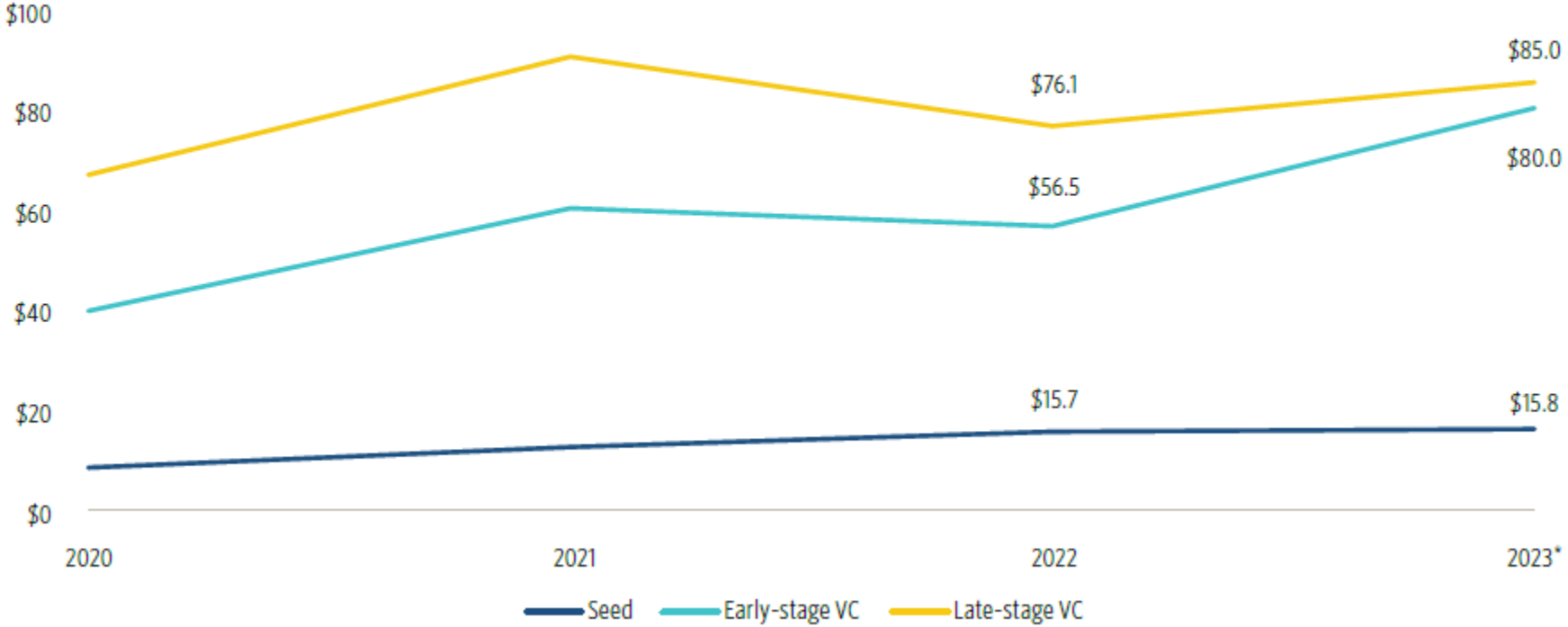
Keting Chu
Chief Executive Officer
BlueJay Therapeutics

Pitchbook: Venture Valuations are Rising

Biopharma

Early-stage and late-stage pre-money valuations increase as companies stay private longer

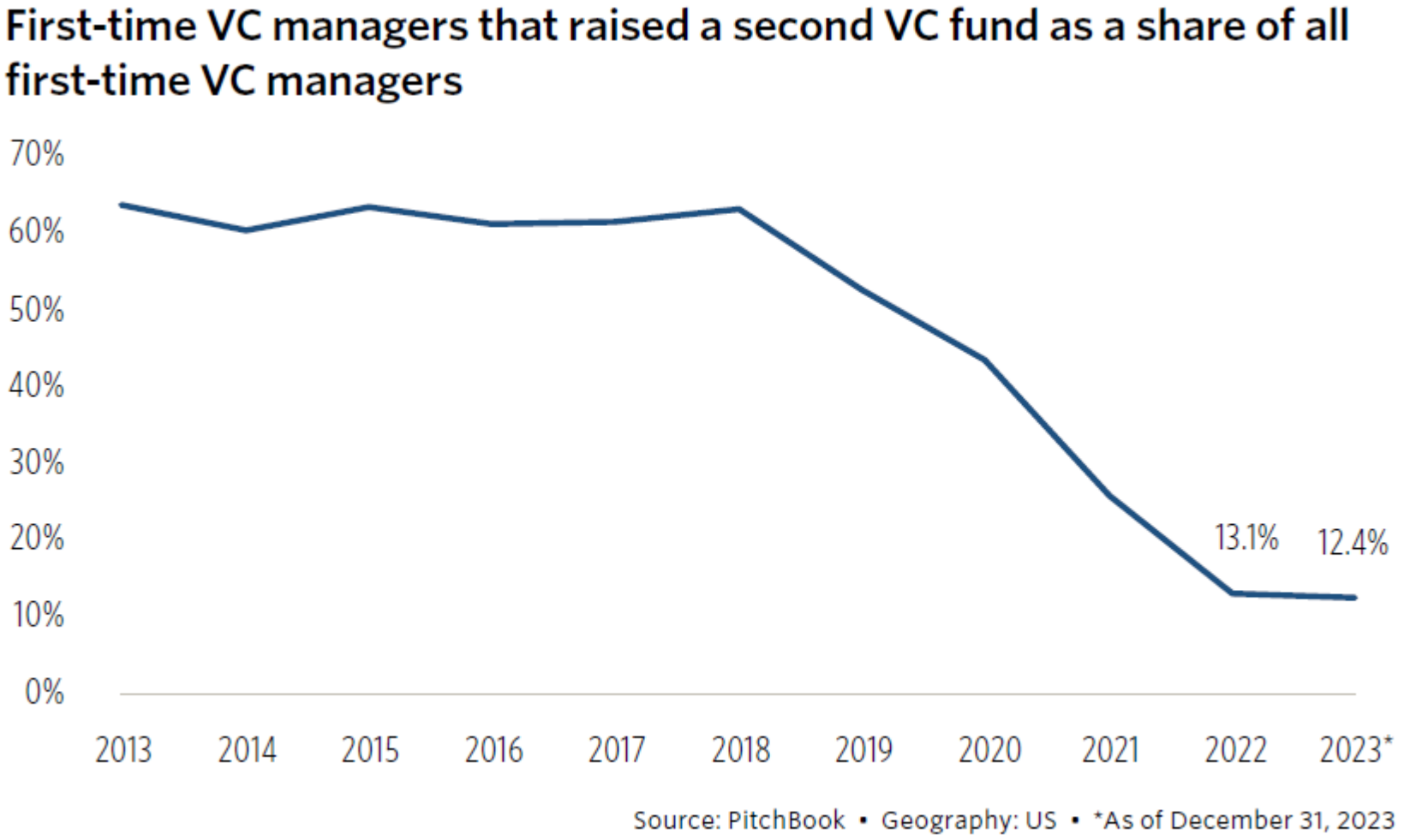
Median biopharma VC pre-money valuation ($M) by stage



Source: PitchBook • Geography: US • *As of December 31, 2023

Source: https://pitchbook.com/news/reports/2023-annual-us-vc-valuations-report

Pitchbook: Getting Harder to Raise a Second Fund



Source: https://pitchbook.com/news/reports/q1-2024-pitchbook-analyst-note-estimating-us-vc-first-time-manager-dropouts

Jim Simons, Math Genius Who Conquered Wall Street, Dies at 86

Jonathan Kandell, "Using advanced computers, he went from M.I.T. professor to multibillionaire. His Medallion fund had 66 percent average annual returns for decades," *New York Times*, May 10, 2024 (excerpt)

Jim Simons, the prizewinning mathematician who abandoned a stellar academic career, then plunged into finance — a world he knew nothing about — and became one of the most successful Wall Street investors ever, died on Friday in his home in Manhattan. He was 86.

His death was confirmed by his spokesman, Jonathan Gasthalter, who did not specify a cause.

After publishing breakthrough studies in mathematics that would play a seminal role in quantum field theory, string theory and condensed matter physics, Mr. Simons decided to apply his genius to a more prosaic subject — making as much money as he could in as short a time as possible.

So, at age 40 he opened a storefront office in a Long Island strip mall and set about proving that trading commodities, currencies, stocks and bonds could be nearly as predictable as calculus and partial differential equations. Spurning financial analysts and business school graduates, he hired like-minded mathematicians and scientists.

Mr. Simons equipped his colleagues with advanced computers to process torrents of data filtered through mathematical models, and turned the four investment funds in his new firm, Renaissance Technologies, into virtual money printing machines.

Source: https://www.nytimes.com/2024/05/10/business/dealbook/jim-simons-dead.html

Jim Simons Was a Major Supporter of Biotech

Richard Teitelbaum

A Jim Simons Market Mystery — Solved?

A secretive investment fund backed by the legendary quant displays a penchant for biotech stocks. There's a good reason for that.

February 7, 2023 Institutional investor

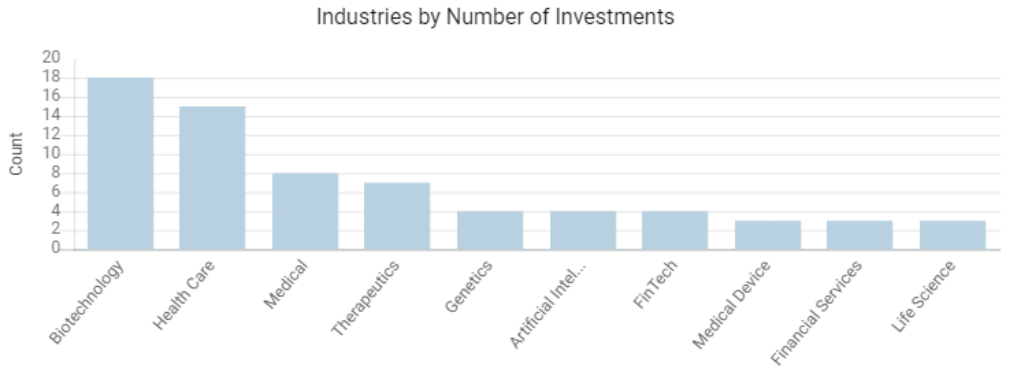
Is Jim Simons, founder of Renaissance Technologies and quant whiz extraordinaire, really a closet stock-picker?

The question springs to mind on account of an investment fund backed by Simons called Euclidean Capital, which is widely reported to be his family office. The fund reports at least some of its public stock holdings quarterly in Securities and Exchange Commission filings.

Euclidean itself is a cipher — with no ready information on its assets, strategy, or how closely Simons is involved. He launched the fund as he stepped down as CEO of Renaissance in 2010, according to one person close to the firm.

The fund has disclosed ownership of ten stocks — mostly biotechnology companies and many lacking revenues. The ten positions as of October 30 totaled just $107.7 million, though that is likely only a part of the fund.

Crunchbase reports that Jim Simons' Family Office, Euclidian Capital made 31 investments in biotech and life sciences companies between 2016 and 2024



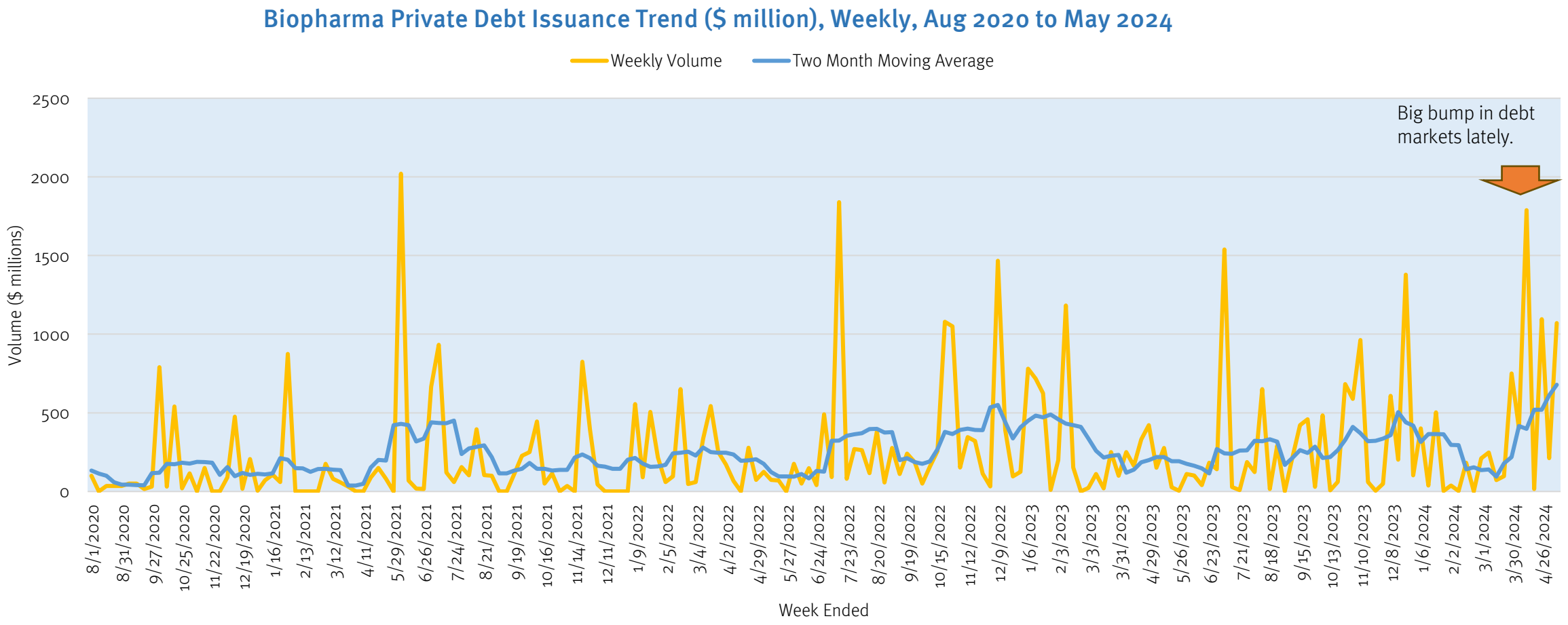
Jim Simons was a major supporter of biotech companies and is likely to continue to be so – posthumously – through Euclidian Capital. Recent investments have been in cell therapy and neuroscience, Kenai and Neurona, two very promising companies.

He has been a major supporter of research in autism. The Simons Foundation Autism Research Initiative (SFARI) has a budget of approximately $90 million per year. Since 2003, the Simons Foundation has provided or committed more than $570 million in external research support to more than 600 investigators in the U.S. and abroad.

Sources: https://www.institutionalinvestor.com/article/2bstqvrdta4idnpqc3hmo/portfolio/a-jim-simons-market-mystery-solved, https://www.sfari.org/about

Biopharma Private Debt Market On Fire Last Week

Last was an exceptionally busy week for the private debt market with $1.1bn issued across nine different offerings. Funds are rushing to put out capital knowing that long-term rates are likely to be coming down in the months ahead. The last five weeks have been the most active for the private debt market since mid 2020.



Source: Data from CapitalIQ, Crunchbase, Stifel research.

Royalty Pharma to Acquire Royalty Interest in Sanofi's Frexalimab for $525 Million

NEW YORK, NY, May 9, 2024 – Royalty Pharma plc (Nasdaq: RPRX) announced today that it will acquire royalties and milestones on frexalimab owned by ImmuNext, Inc. (ImmuNext) for approximately $525 million in cash including estimated transaction costs. ImmuNext, a privately-held biotechnology company, is entitled to a royalty on net sales of frexalimab and milestones related to the achievement of regulatory and clinical events and commercial sales.

Frexalimab, in development by Sanofi, is a first-in-class, second generation anti-CD40 ligand monoclonal antibody. Frexalimab is in three Phase 3 clinical studies for the treatment of multiple sclerosis (MS). Phase 2 clinical studies for systemic lupus erythematosus and Type 1 Diabetes are ongoing. Sanofi stated that potential non-risk-adjusted peak sales for frexalimab may be greater than €5 billion (December 7, 2023 R&D Day). Sanofi anticipates filing a biologics license application (BLA) for relapsing multiple sclerosis with the U.S. Food & Drug Administration in 2027. Worldwide sales of MS therapies amounted to approximately $25 billion in 2023 according to IQVIA.

Pablo Legorreta, Royalty Pharma's founder and Chief Executive Officer said, "This transaction will expand our attractive and growing development-stage portfolio with a next-generation immunology therapy. Frexalimab has the potential to achieve high efficacy without the chronic depletion of the immune system commonly associated with currently available MS therapies. In light of frexalimab's exciting Phase 2 study results in MS and its significant potential in a wide range of immune-mediated diseases, we believe frexalimab is a potentially transformative therapy for patients."

Following this transaction, Royalty Pharma will have 15 therapies in its development-stage portfolio, 11 of which will be in Phase 3 development or undergoing regulatory review. In aggregate, on a non-risk adjusted basis, Royalty Pharma's development-stage pipeline will have the potential to generate combined peak royalties significantly greater than $1 billion per year.

Source: https://www.royaltypharma.com/news/royalty-pharma-to-acquire-royalty-interest-in-sanofis-frexalimab/

Ligand and Agenus Enter Into $100 Million Royalty Financing Agreement

JUPITER, Fla. and LEXINGTON, Mass.--(BUSINESS WIRE) – Ligand Pharmaceuticals Incorporated (Nasdaq: LGND) and Agenus Inc. (Nasdaq: AGEN), a leader in discovering and developing novel immunological agents to treat various cancers, today announced that the companies have entered into a royalty financing agreement to support Agenus' key development initiatives in the ongoing BOT/BAL clinical development program, including its planned confirmatory Phase 3 trial in its lead indication of patients with metastatic, relapsed/refractory colorectal cancer not microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR), who are without active liver metastases (r/r MSS CRC NLM), along with other launch readiness activities.

Under the terms of the agreement, Ligand will pay $75 million to Agenus at closing. In addition, Ligand has the option to invest an additional $25 million on the same terms on a pro rata basis. In return for the initial $75 million payment, Ligand will receive 18.75% of the future royalties and 31.875% of the future milestone payments related to six of Agenus' clinical-stage partnered oncology programs, including BMS-986442 (Bristol Myers Squibb), AGEN2373 (Gilead Sciences), INCAGN2385 and INCAGN2390 (Incyte), MK-4830 (Merck), and UGN-301 (UroGen Pharma). Ligand's portion of the milestones related to these six programs has the potential to exceed $400 million, with royalties in the low single digits. In addition, Ligand will also receive a 2.625% royalty on future global net sales generated by BOT/BAL. The royalties and milestone payments owed to Ligand could be adjusted up or down based upon pre-determined future events and achievements of certain milestones.

As part of the agreement, the companies have also agreed to allow Agenus to syndicate up to an additional $125 million, potentially bringing the total capital infusion up to $200 million. This strategic collaboration will further validate BOT/BAL's potential as a transformative treatment for patients with solid tumor malignancies and enhances Agenus' ability to advance this promising therapy.

Garo Armen, Chairman and Chief Executive Officer of Agenus, commented, "We are pleased to partner with Ligand, a company that recognizes the paradigm-shifting potential of BOT/BAL in delivering benefit to patients across the solid tumor landscape. Ligand also recognizes the potential impact of our ongoing partnered programs, many of which are showing promise in the clinic. This collaboration enables both parties to benefit in the future potential success of these assets while simultaneously enabling Agenus to accelerate our efforts to bring BOT/BAL to patients in need."

Source: https://investor.ligand.com/news-and-events/press-releases/news-details/2024/Ligand-and-Agenus-Enter-Into-100-Million-Royalty-Financing-Agreement/default.aspx

Karyopharm Announces Significant Refinancing Transactions and Amended Royalty Agreement

NEWTON, Mass., May 8, 2024 – Karyopharm Therapeutics Inc. (Nasdaq: KPTI), a commercial-stage pharmaceutical company pioneering novel cancer therapies, announced today that it has entered into a series of financing transactions that will extend the Company's debt maturities into 2028 and 2029, well beyond the Company's planned Phase 3 data readouts in 2025.

"We are extremely pleased to have accomplished several important objectives for Karyopharm and our shareholders with this refinancing. We successfully strengthened our balance sheet by extending the maturity of the vast majority of our debt obligations well beyond the planned readouts and potential approvals of our three ongoing Phase 3 programs," said Richard Paulson, President and Chief Executive Officer of Karyopharm. "With the demonstrated strong commitment from HealthCare Royalty and our top convertible note holders, we have enhanced our ability to unlock the potential of selinexor."

As part of these refinancing transactions, on May 8, 2024, the Company entered into privately negotiated agreements with certain funds managed by each of Braidwell LP, Highbridge Capital Management, LLC, Davidson Kempner Capital Management LP and Context Capital Management, the top four holders of the Company's outstanding 3.0% Convertible Notes due 2025 (the 2025 Convertible Notes) to exchange approximately $148.0 million aggregate principal amount out of the $172.5 million aggregate principal amount of the 2025 Convertible Notes then outstanding for approximately $111.0 million aggregate principal amount of the Company's newly issued 6.0% Convertible Notes due 2029 (the 2029 Convertible Notes), plus warrants to purchase up to approximately 46.0 million shares of the Company's common stock, at an exercise price of $1.10 per share. Exchanging holders will receive 2029 Convertible Notes having a principal amount equal to 75% of the principal amount of 2025 Convertible Notes exchanged by them (i.e., $750 in principal amount of 2029 Convertible Notes for each $1,000 in principal amount of 2025 Convertible Notes surrendered in exchange). The 2029 Convertible Notes will be secured on a second-lien basis by the same collateral that secures the Secured Term Loan.

New $100.0 Million Senior Secured Term Loan

On May 8, 2024 (the Term Loan Closing Date), the Company also entered into a new $100.0 million first lien senior secured term loan facility (the Secured Term Loan). The lenders under the Secured Term Loan include certain holders of the 2025 Convertible Notes and HCRx, with existing holders of the 2025 Convertible Notes funding $85.0 million and HCRx funding $15.0 million through satisfaction of approximately $15.0 million of the Company's existing obligations to HCRx. The Secured Term Loan matures in May 2028 and accrues interest at a rate of Secured Overnight Financing Rate (SOFR) plus 9.25%. Amortization payments will commence 24 months after closing.

Source: https://investors.karyopharm.com/2024-05-08-Karyopharm-Announces-Significant-Refinancing-Transactions-and-Amended-Royalty-Agreement-Extending-Vast-Majority-of-Its-Debt-Maturities-into-2028-and-2029

Verona Pharma Announces $650 Million Strategic Financing with Oaktree and OMERS

LONDON and RALEIGH, N.C., May 09, 2024 (GLOBE NEWSWIRE) – Verona Pharma plc (Nasdaq: VRNA) ("Verona Pharma"), announces it and its wholly-owned subsidiary, Verona Pharma, Inc. ("VPI" and together with Verona Pharma, the "Company"), have entered into strategic financing agreements providing access to up to $650 million from funds managed by Oaktree Capital Management, L.P. ("Oaktree") and OMERS Life Sciences ("OMERS").

The agreements provide non-dilutive capital and additional financial flexibility ahead of Verona Pharma's planned US launch of ensifentrine and will support the Company's continued growth. Ensifentrine is currently under review by the US Food and Drug Administration ("FDA"), and, if approved, is expected to be the first novel inhaled mechanism for the maintenance treatment of chronic obstructive pulmonary disease in more than 20 years.

The strategic financing was led by Oaktree and is comprised of the following:

- Debt facility: Up to $400 million in term loans available in five separate tranches via a term loan facility ("debt facility").
- Revenue interest purchase and sale agreement ("RIPSA"): Up to $250 million in funding from the sale of a redeemable interest in future ensifentrine-related revenue, which is capped at 1.75x of the amount funded.

The debt facility replaces the existing facility of up to $400 million with funds managed by Oxford Finance LLC and Hercules Capital, Inc. (NYSE: HTGC).

Under the terms of the debt facility, VPI is drawing $55 million at closing, and may draw, subject to certain conditions, an additional $70 million upon FDA approval of ensifentrine, $175 million in two separate tranches upon achievement of certain net sales milestones and, subject to the approval of the Lenders, $100 million to support strategic initiatives. VPI will pay only interest on the outstanding loans under the five-year debt facility on a quarterly basis with all amounts outstanding due at maturity. Approximately $52 million of the loans drawn at closing will be used to repay in full the existing facility, including to pay fees and associated costs thereunder.

Under the terms of the RIPSA, VPI will receive $100 million upon FDA approval of ensifentrine and will be eligible to draw an additional $150 million upon the achievement of certain net sales milestones. The revenue interest financing rate is 5% and 6.5% of certain proceeds the Company receives from licensees that the Company may engage during the term of the RIPSA outside of the US and in the US, respectively, and 6.5% of global net sales of ensifentrine by the Company. The total revenue interest financing payable by the Company to Oaktree and OMERS is capped at 1.75x of the amount actually funded, with the ability to redeem the RIPSA at lower multiples within the first three years from funding.

Source: https://www.veronapharma.com/media/verona-pharma-announces-650-million-strategic-financing-oaktree

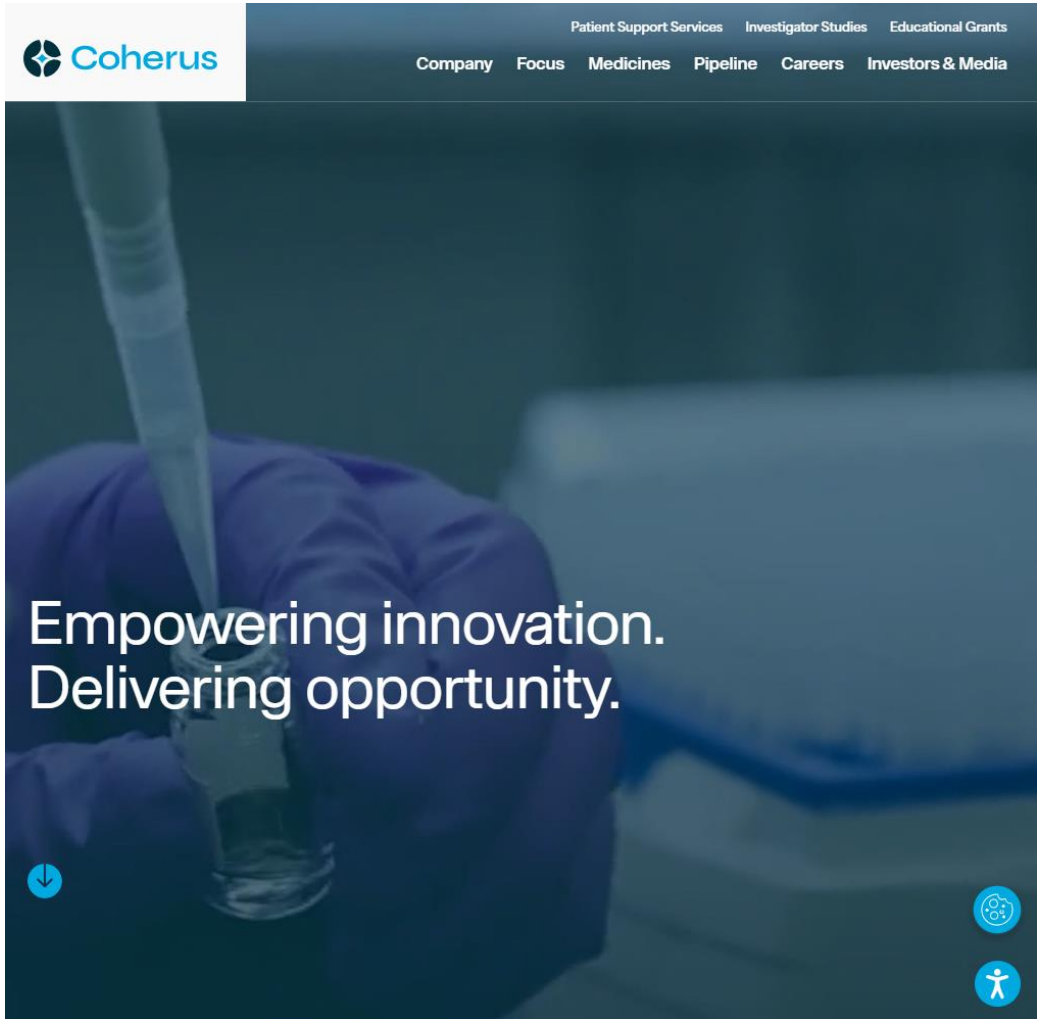
Coherus Announces Full Repayment of Pharmakon $75 Million Term Loan

REDWOOD CITY, Calif., May 09, 2024 – Coherus BioSciences, Inc. (Coherus, Nasdaq: CHRS), today announced it entered into a combined term loan and product royalty financing agreement with Barings that has allowed Coherus to fully pay off the remaining $75 million of its Pharmakon Advisors term loan. This further reduces the Company's term loan debt by approximately half, with an extended loan maturity date of May 2029.

"This debt and royalty financing arrangement fully repays the $75 million remaining on our prior $250 million term loan that was due in October 2025," said Denny Lanfear, Chief Executive Officer of Coherus. "This transaction improves our capital structure, moves the maturity date to a point more consistent with our development horizon, setting us on the course of long-term, sustainable growth as a focused oncology company."

Under the terms of the royalty monetization facility, Coherus received $37.5 million in return for a certain net sales royalty percentage consideration on U.S. sales of LOQTORZI® and UDENYCA® up to a hard cap. Under the term loan, Coherus received $38.7 million in proceeds from a structured debt loan with a May 2029 maturity.

Barings LLC is a global asset management firm supporting leading businesses with flexible financing solutions.



Source: https://investors.coherus.com/news-releases/news-release-details/coherus-announces-full-repayment-pharmakon-advisors-75-million

Sobi has Completed SEK 3 Billion ($276mm) Senior Bond Issue

May 8, 2024

Swedish Orphan Biovitrum AB (publ) (Sobi®) has successfully completed the inaugural issue of senior unsecured bonds of SEK 3 billion under its newly established MTN programme.

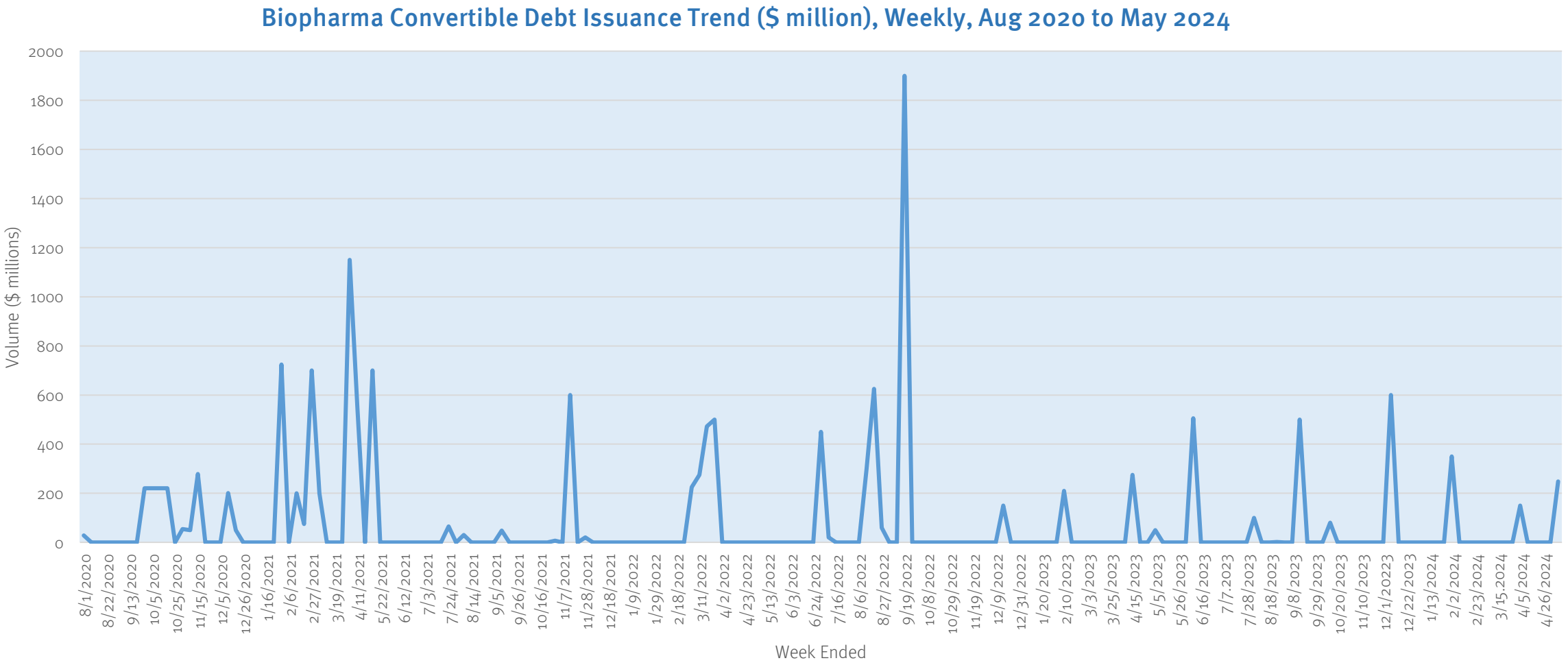
The bonds are divided into three tranches where SEK 1.35 billion was issued with a tenor of 3 years and carries a floating rate of 3-months STIBOR + 1.35%, SEK 1.10 billion was issued with a tenor of 5 years and carries a floating rate of 3-months STIBOR + 1.75% and SEK 550 million was issued with a tenor of 5 years and carries a fixed rate of 4.515%.

The bond issue generated strong investor interest and was oversubscribed.

Source: https://www.sobi.com/en/press-releases/sobi-has-completed-sek-3-billion-senior-bond-issue-2230701

Pacira Accessed Convertible Bond Market Last Week

Last week saw Pacira issue a $275 million convertible bond. These types of issues have been relatively rare.

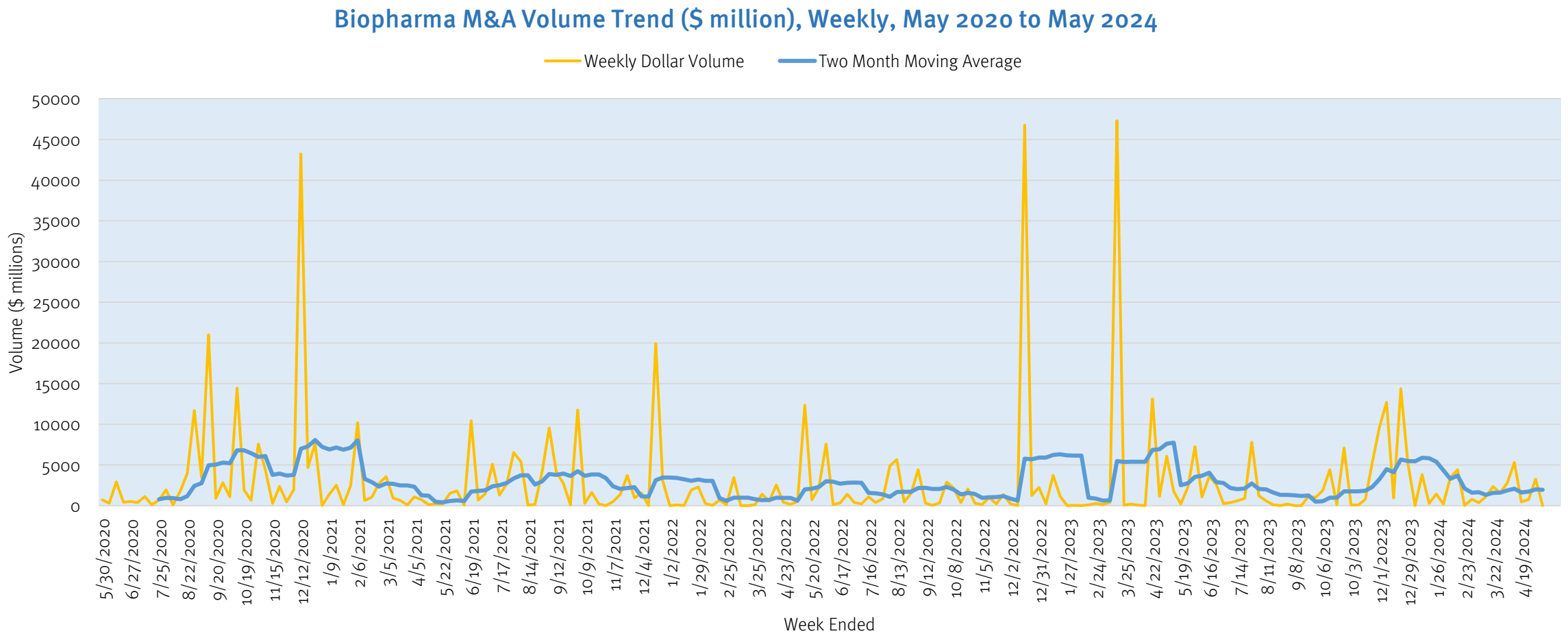


Source: Data from CapitalIQ, Crunchbase, Stifel research.

Deal News

Last Week Saw No Meaningful M&A Volume

Last week saw an increased offer for Vanda Pharma and the acquisition of Serendipity, a gene editing biotech by Arbor Biotechnologies. It was a very quiet week for M&A.



Source: S&P, CapitalIQ

Novavax Soars on $1.4B Deal With Sanofi for COVID Vaccine

Kate Goodwin, *Biospace*, May 10, 2024 (excerpt)

Sanofi announced a deal worth up to $1.4 billion with Novavax on Friday for its COVID-19 vaccine, giving the Maryland-based biotech a much-needed boost to its struggling business.

The French pharma is dropping $500 million upfront for Novavax's COVID-19 vaccine, with the goals of co-commercializing its current formulation as well as developing a combination vaccine for COVID and flu. An additional $700 million is up for grabs in milestone payments. Along with another potential $200 million in milestones for additional vaccines made with Novavax's Matrix adjuvant technology, deal totals $1.4 billion—more than double the biotech's current market cap of $627 million.

Thanks to the infusion of cash, Novavax will be able to lift its prior warning to investors issued in February 2023 expressing doubts over its ability to stay in business, its CEO John Jacobs told CNBC News. The deal skyrocketed Novavax's stock Friday morning in premarket trading, up 120% at one point. In February 2024, the stock had dropped over 25% after the biotech's fourth quarter earnings missed estimates.

From Sanofi's perspective, Head of Vaccines R&D Jean-Francois Toussaint emphasized the value of targeting COVID and flu with one shot. Sanofi has three mRNA candidates now in clinical testing for RSV, flu and a combination of the two. And already on the market are two quadrivalent influenza vaccines from the company, which has not yet been disclosed what shot will be combined with Novavax's protein-based one.

"With flu and COVID-19 hospital admission rates now closely mirroring each other, we have an opportunity to develop non-mRNA flu-COVID-19 combination vaccines, offering patients both enhanced convenience and protection against two serious respiratory viruses," Toussaint said in a statement.

This deal is great news for the vaccine sector, giving a major helping hand to struggling Novavax. On the other hand, it was a very bad day for short sellers.

One will note on p. 15 that Novavax is the second most shorted life sciences company. The 98% bump in Novavax shares on Friday would have caused a major mark-to-market loss for funds that shorted this stock.

Source: https://www.biospace.com/article/novavax-soars-on-1-4b-deal-with-sanofi-for-covid-vaccine-/

After FTC Stalled Sanofi Deal, Shionogi Secures Maze's Pompe Disease Drug for $150M

James Waldron, *FierceBiotech*, May 10, 2024 (excerpt)

It appears Sanofi's loss is Shionogi's gain. Five months after the Federal Trade Commission (FTC) scuttled Sanofi's attempt to acquire Maze Therapeutics' Pompe disease program, Japan's Shionogi has scooped up the asset.

Maze and Sanofi unveiled their own licensing deal for the program, MZE001, back in May 2023. The French pharma agreed to pay $150 million upfront along with the potential for $605 million in milestones for worldwide rights to a drug candidate that could treat Pompe by stopping the buildup of glycogen.

It looked like a good fit for Sanofi's pipeline, where MZE001 would have sat alongside another Pompe treatment in the form of enzyme replacement therapy Nexviazyme. But the FTC saw that as a problem, arguing that the deal would "eliminate a nascent competitor poised to challenge Sanofi's monopoly in the Pompe disease therapy market."

While Sanofi objected to the move, it didn't formally contest the agency's decision. By December 2023, the drugmaker had announced it was terminating the agreement.

Step forward, Shionogi, which revealed this morning that it has acquired MZE001 for itself for the same upfront price tag of $150 million. While milestone payments are also attached to the deal, the precise amount wasn't disclosed in the May 10 release.

Source: https://www.fiercebiotech.com/biotech/after-ftc-stalled-sanofi-deal-shionogi-secures-mazes-pompe-drug-105m

Industry News

House's Updated Biosecurity Bill Sets 2032 Deadline

Angus Liu, *FierceBiotech*, May 10, 2024 (excerpt)

Right after an industry survey suggested that switching away from Chinese CDMOs could take biopharma companies up to eight years, lawmakers have adjusted the BIOSECURE Act. The new draft lays out a 2032 deadline for the separation mandate.

The House version of the BIOSECURE Act has been amended to grandfather existing contracts that drug developers may have with five China-related biopharma service providers, including both WuXi Apptec and its sister contract manufacturer WuXi Biologics. Those relationships, including negotiated option years, are now exempt from national security scrutiny under the proposed legislation until Jan. 1, 2032, according to the revised bill seen by Fierce Pharma.

The House Oversight Committee is expected to mark up the bill on May 15. In an unusually swift action, House leadership is considering reserving a floor vote for the BIOSECURE Act this month, Axios reports. In March, the Senate Homeland Security Committee voted to advance a counterpart bill to the Senate floor.

The update to the House bill was welcome news to the biopharma industry.

In a statement on Thursday, Biotechnology Innovation Organization's CEO, John Crowley, praised the updated bill for providing "a reasonable timeframe for companies to decouple their reliance on China-based biomanufacturing."

Source: https://www.fiercepharma.com/pharma/houses-updated-biosecurity-bill-sets-decoupling-deadline-chinese-cdmo-end-2031

Drugmakers Race to Find Alternative Suppliers as US Cracks Down on Chinese Biotech

Oliver Barnes, Ian Johnston and Eleanor Olcott, *Financial Times*, May 11, 2024 (excerpt)

Western pharmaceutical companies are in talks with alternative suppliers in response to draft US legislation seeking to restrict an important Chinese drug developer and manufacturer over national security concerns.

The Biosecure Act would prohibit US companies receiving federal grant money from working with four Chinese biotech companies, including WuXi AppTec and its sister company WuXi Biologics, which produce active pharmaceutical ingredients (API) for hundreds of US and European drugmakers.

Companies, including US-based Eli Lilly, Vertex Pharmaceuticals and BeiGene in Switzerland, have been talking with rival contract manufacturers to diversify production away from WuXi companies, according to several people familiar with discussions.

“Everyone is reaching out to alternative [contract development manufacturing organisations] right now,” said an executive at a US-based drug outsourcer, which competes with WuXi. “The companies’ management teams have an obligation to ask if the Biosecure Act gets approved what is their plan B?

”BeiGene said it was “finalising a second source of API outside of China” as part of a process that began in 2019. Eli Lilly and Vertex declined to comment on the talks.

Biotechnology has become one of Washington’s national security priorities, as the Biden administration works to onshore manufacturing capacity as well as slow China’s access to sophisticated technology, including semiconductors.

The bill labels Shanghai-based WuXi AppTec “a biotechnology company of concern”, which is described as any entity posing a risk to the US by engaging in joint research with a foreign adversary’s military, providing data obtained through equipment, and obtaining human data through equipment and services without informed consent.

Source: https://www.ft.com/content/bfe48705-5610-4b6d-bbe4-0844f50483b2

Japan's Takeda Pharma to Restructure after Annual Profit Slump

***Reuters*, May 9, 2024**

Japan's Takeda Pharmaceutical announced a restructuring on Thursday after annual profit slid by more than half following the loss of patent protection of major sellers.

Japan's biggest drugmaker said it will incur restructuring costs of about 140 billion yen ($899 million) this fiscal year as part of a plan to optimise its workforce, cut costs and strengthen technology.

A spokesman said there was not a specific headcount number that may be reduced in the plan, which is to be phased in "according to unique business needs and country requirements".

Operating profit was 214.1 billion yen for the 12 months through March, versus 490.5 billion yen last year and a consensus estimate of 265.3 billion yen in an LSEG survey of 13 analysts.

Takeda forecast operating profit will reach 225 billion yen in the current fiscal year.

The drugmaker had flagged fiscal 2023 as a rebuilding phase as it lost exclusivity on blood pressure drug Azilva in Japan and hyperactivity treatment Vyvanse in the United States.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/japans-takeda-pharma-says-full-year-profit-slumps-56-2024-05-09/

Vertex Posts Strong Quarter

Q1 2024 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q1 23	FY 23	Q1 24
Total CF product revenues	$2.37B	$9.87B	**$2.69B**
TRIKAFTA/KAFTRIO	2.10B	8.94B	**2.48B**
Other CF products	278	925	**207**
Combined non-GAAP R&D, acquired IPR&D and SG&A expenses	1.21B	4.24B	**1.02B**
Non-GAAP operating income	902	4.37B	**1.34B**
Non-GAAP operating margin %	38%	44%	**50%**
Non-GAAP net income	794	3.97B	**1.24B**
Non-GAAP net income per share – diluted	$3.05	$15.23	**$4.76**
Cash, cash equivalents & total marketable securities (period-end)	$11.5B	$13.7B	**$14.6B**

Source: https://investors.vrtx.com/events/event-details/vertex-pharmaceuticals-q1-2024-conference-call

Vertex Pipeline and Future Catalysts Impressive

RECENT HIGHLIGHTS	ANTICIPATED KEY MILESTONES
• **KALYDECO received European Commission approval** in infants with CF ages 1 mo to <4 mo • **Vanza triple combo therapy: Completed NDA submissions to FDA and EMA** in patients ages 6+ • **VX-522 CFTR mRNA study: MAD portion enrolling and dosing patients**	• **Continue to reach more eligible patients;** expand into younger age groups • **Vanza triple: Prepare for potential launch in multiple geographies** • **VX-522: Complete MAD portion** of the study; data late 2024/early 2025

• **CASGEVY:**
  • **Received regulatory approvals** in SCD and TDT in multiple countries
  • **Regulatory reviews ongoing** in Canada (priority review) and Switzerland for SCD and TDT
	• **CASGEVY:**
	  • **Reach more eligible patients across approved geographies**
	  • **Secure additional global regulatory approvals**

• **Suzetrigine:**
  • **Acute pain: Began rolling NDA submission;** multiple modules submitted
  • **DPN: Completed successful End-of-Phase 2 meeting with FDA**
  • **LSR: Advance Phase 2 study**
• **VX-993: Completed Phase 1 study (oral); IND cleared (IV) and Phase 1 study initiated**
	• **Suzetrigine:**
	  • **Acute: Complete rolling NDA submission in Q2:24; prepare for potential U.S. launch**
	  • **DPN: Initiate Phase 3 program in H2:2024**
	  • **LSR: Complete Phase 2 study enrollment by year-end**
	• **VX-993: Initiate acute pain Phase 2 study (oral); complete Phase 1 study (IV)**
	• **VX-993: Initiate neuropathic pain Phase 2 study (oral)**

• **Inaxaplin (AMKD): Selected dose and advanced into Phase 3 portion of Phase 2/3 clinical trial** • **VX-407 (ADPKD): Initiated Phase 1 clinical trial in healthy volunteers**	• **Inaxaplin: Continue to enroll and dose patients in Phase 3** • **VX-407: Complete Phase 1 study**
• **VX-880 (T1D): Phase 1/2 trial fully enrolled** (Parts A, B, C study of 17 patients); resumed dosing • **VX-264: Part B of Phase 1/2 trial underway**	• **VX-880: Complete dosing in Part C; present data at ADA in June 2024** • **VX-264: Enroll and dose patients in Part B**
• **VX-670 (DM1): Phase 1/2 clinical trial enrolling and dosing DM1 patients** in multiple regions	• **Continue to enroll and dose patients**
• **Alpine Immune Sciences acquisition announced**	• **Close Alpine acquisition**; post-closing, advance povetacicept into Phase 3 study in IgAN + multiple data readouts from ongoing Phase 2 basket studies in autoimmune renal diseases and cytopenias

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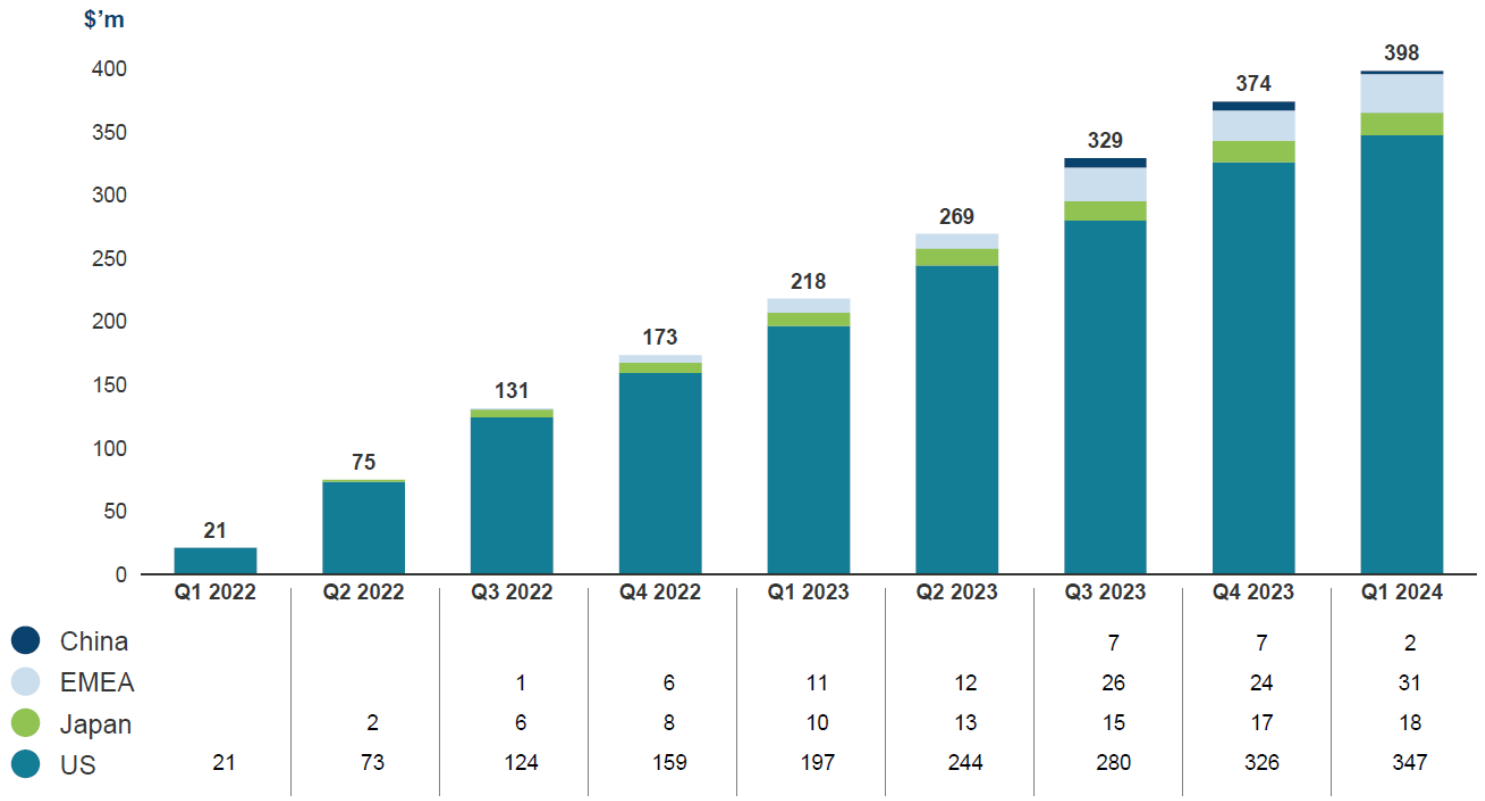
Source: https://investors.vrtx.com/events/event-details/vertex-pharmaceuticals-q1-2024-conference-call

argenx Revenue Growth Slows in Q1 2024

Product Net Sales: 2024 Q1 of $398 million



Q1 2024: growth of 83% vs Q1 2023

(in millions of $)	Q1 2024	Q1 2023	Growth %
US	347	197	76%
Japan	18	10	80%
EMEA	31	11	180%
China	2	0	-
Total	**398**	**218**	**+83%**

Q1 2024: growth of 6% vs Q4 2023

(in millions of $)	Q1 2024	Q4 2023	QoQ % Growth
US	347	326	7%
Japan	18	17	4%
EMEA	31	24	28%
China	2	7	-68%
Total	**398**	**374**	**+6%**

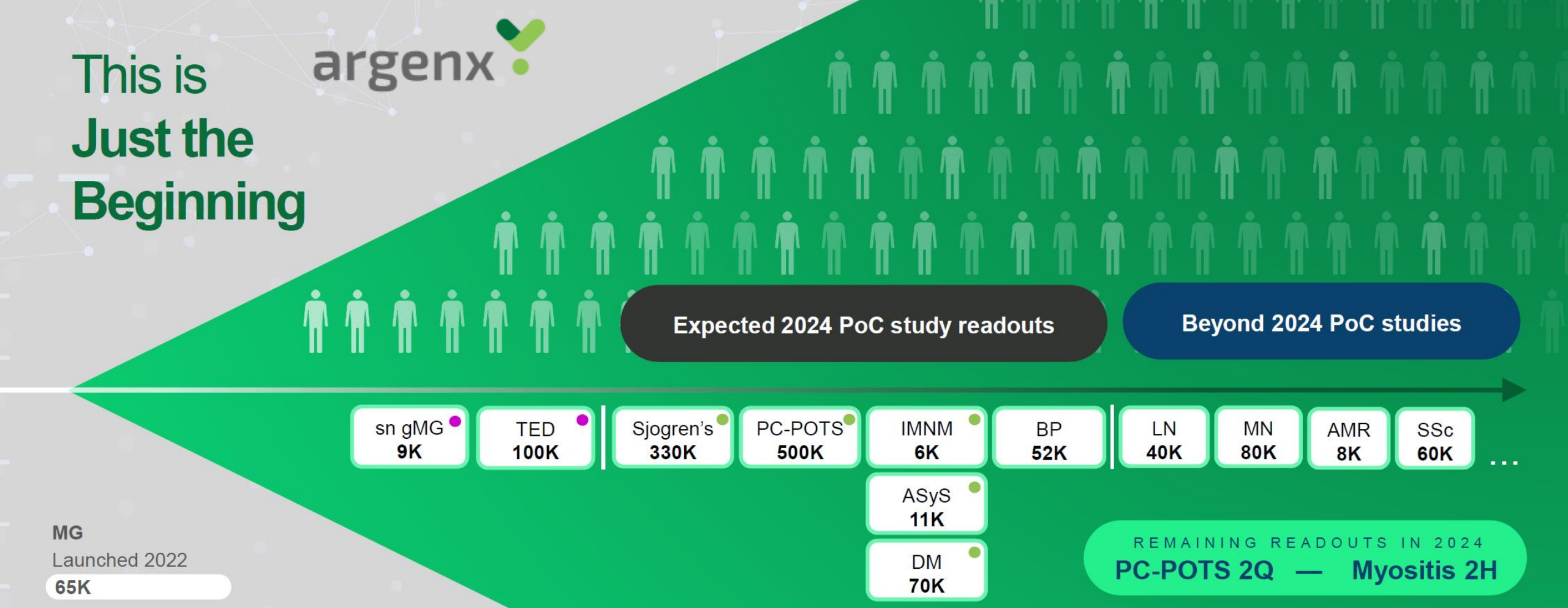
Source: https://www.us.argenx.com/sites/default/files/event-attachment/ARGX_1Q_2024_Financial_and_BusinessUpdate.pdf

VYVGART® (efgartigimod alfa-fcab) Injection for Intravenous Use 400 mg/20 mL vial

VYVGART® Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) Subcutaneous Injection 180 mg/mL and 2000 U/mL vial

This is Just the Beginning

argenx



REMAINING READOUTS IN 2024

PC-POTS 2Q — Myositis 2H

MG

Launched 2022

65K

CIDP

FDA PDUFA | June 21, 2024

24K

ITP

Approved in Japan | March 26, 2024

17K

● Phase 2 Proof of Concept ● 2024 Phase 3 Start

*** argenx market research; US prevalence numbers (except Japan ITP)

Source: https://www.us.argenx.com/sites/default/files/event-attachment/ARGX_1Q_2024_Financial_and_BusinessUpdate.pdf

Competitive Update: JCI Insight Publication Last Week Shows that Nipocalimab Analogue Associated with Albumin Reduction

This paper compares the Dyax/Momenta/J&J FcRn scaffold to that of efgartigimod and that of Hanall/Immunovant's Batocalimab. Batocalimab is associated with substantial downregulation of albumin. The J&J Nipocalimab scaffold has the same effect but not to the same degree. The Argenx scaffold for efgartigimod does not suppress albumin at all. This publication does not look at Immunovant's IMVT-1402 as its structure has yet to be published. Note that some of the authors here work for argenx.

Ma G, Crowley AR, Heyndrickx L, Rogiers I, Parthoens E, Van Santbergen J, Ober RJ, Bobkov V, de Haard H, Ulrichts P, Hofman E, Louagie E, Balbino B, Ward ES. Differential effects of FcRn antagonists on the subcellular trafficking of FcRn and albumin. *JCI Insight*. May 7, 2024

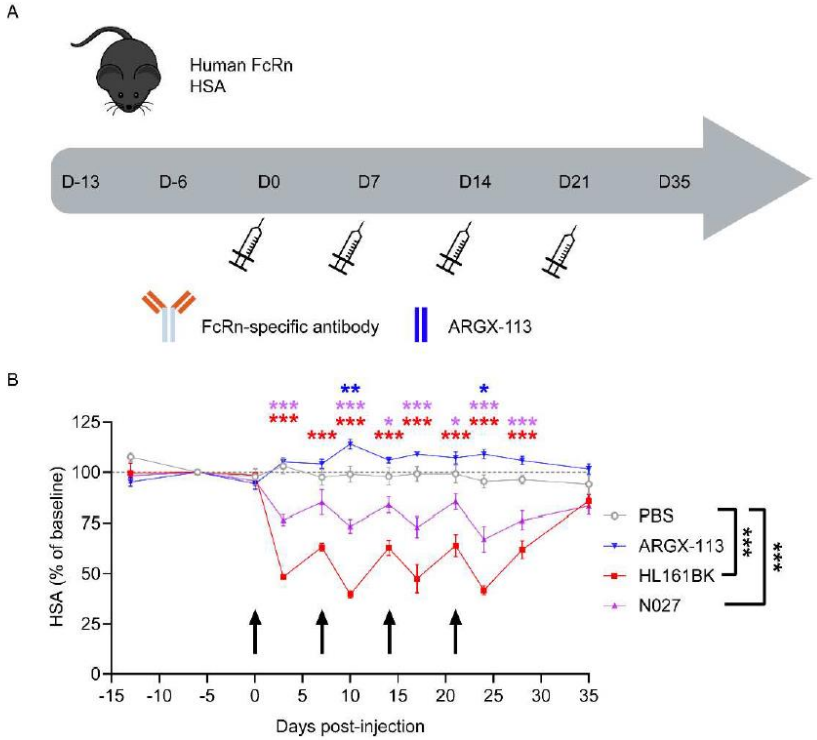


Figure 7. Effects of FcRn antagonists on HSA levels in mice humanized to express hFcRn and HSA
14-15-week-old female or male Albumus Rag1-deficient (KO) mice (C57BL/6N-*Fcgrt*$^{tm1.1(huFCGRT)Geno}$;*Alb*$^{tm1.1(huALB)Geno}$;*Rag1*^{tm1Geno}) were IP injected with antagonist (100 mg/kg for N027 or HL161BK, n = 5 per treatment group; 35 mg/kg for ARGX-113, n = 8), or PBS (n = 3) on days 0, 7, 14, and 21. 20 µL blood samples were collected to establish baseline levels of endogenous HSA on days -13 and -6 (pre-dose). 20 µL blood samples were collected from each mouse 1 hour after each injection in addition to sampling on days 3, 10, 17, 24, 28, and 35. HSA concentrations were assessed by ELISA. (**A**) Schematic representation of dosing and sample collection. (**B**) HSA levels normalized to day -6, black arrows indicate days of IP injections. Data for PBS, HL161BK, and N027 are representative of two individual experiments (n = 3 for PBS, n = 5 for HL161BK and N027 in each experiment); data for ARGX-113 (n = 8) are from one experiment. Statistical analysis for each day was performed with a longitudinal model and significant differences compared to the PBS control are denoted above each timepoint as: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. One-way ANOVA with Dunnett multiplicity adjustment was used for the analysis of the overall average percentage changes in HSA levels from baseline (PBS control; D0 to D35) for the individual mouse profiles over time, summarized as AUC (significant differences denoted on the right of the key). Error bars indicate the standard error of the mean.

Source: https://insight.jci.org/articles/view/176166

Venrock Publishes Its 2024 Healthcare Prognosis Survey

Brian Roberts and Bob Kocher, Venrock, 2024 Healthcare Prognosis, May 10, 2024

Once again, we tapped into our network of super smart healthcare friends to conduct a pulse-check of sentiment and perspectives around hot topics in healthcare. Looking back at last year's wisdom of the (intelligent) crowd, we missed on several fronts believing that the Fed rates would have dropped by now and only a quarter of us were optimistic that the stock market would end the year up. We were also way off on Ozempic, predicting disillusionment after early adoption.

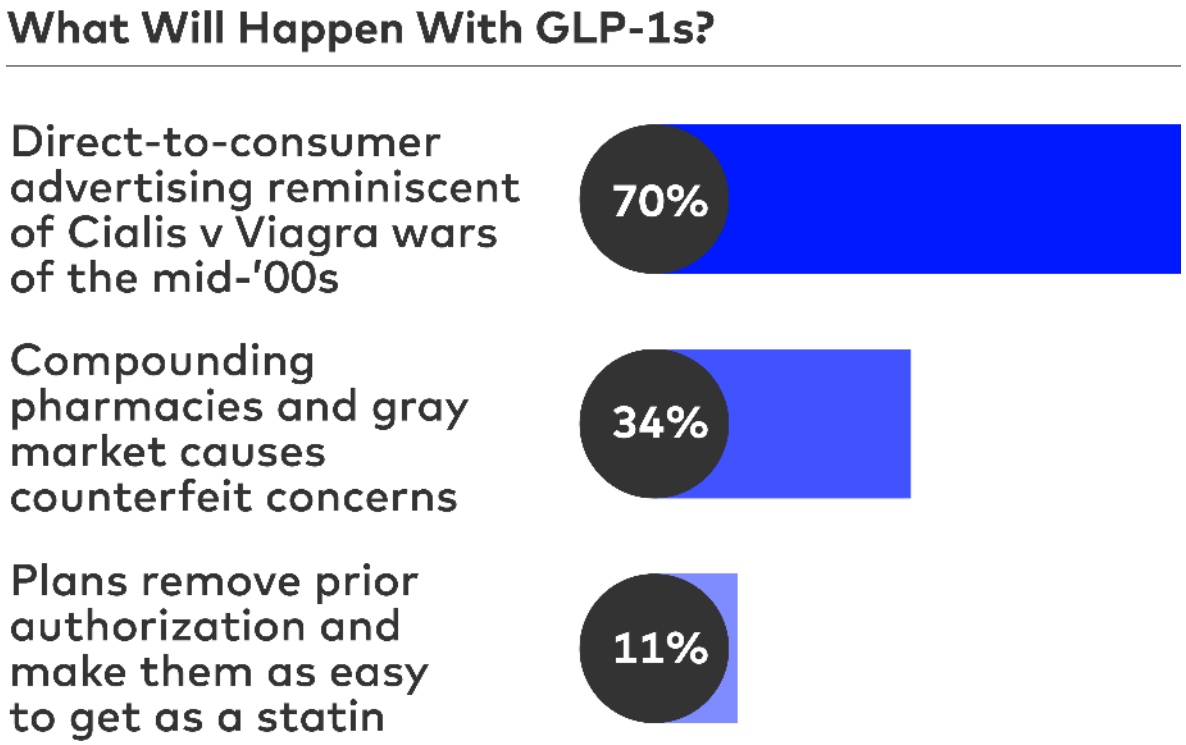
Looking at 2024 views, GLP-1s are firmly consensus, with ever broader clinical benefits, while CMS is expected to make even more headway with drug price negotiations. In the less exciting camp, "talk not translating to action" by the FTC remains the norm - but how about those non-competes! Contrary to last year, almost three quarters of us anticipate a good year for the stock market… three cheers for the optimists!

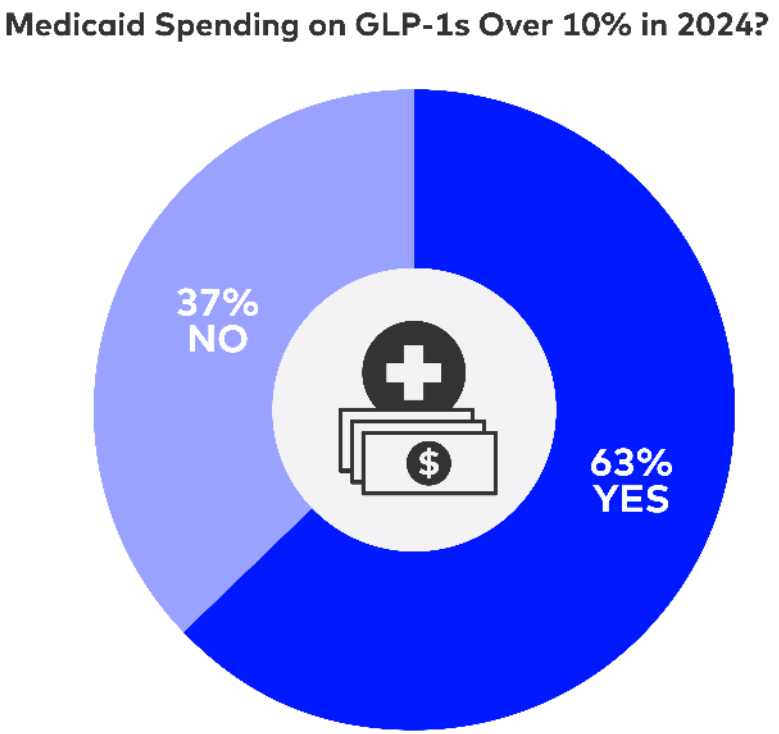
In addition, after our survey closed, Arizona's state Supreme Court applied a 160-year old law to ban nearly all abortions. While the state legislature swiftly repealed said ancient law, it feels like we can pretty confidently call the prediction early that reproductive rights will continue to erode in many states, and give it to the 63% "yes" votes.

Source: https://hcprognosis2024.venrock.com/

Venrock: Respondents See GLP-1's Becoming Big DTC Items

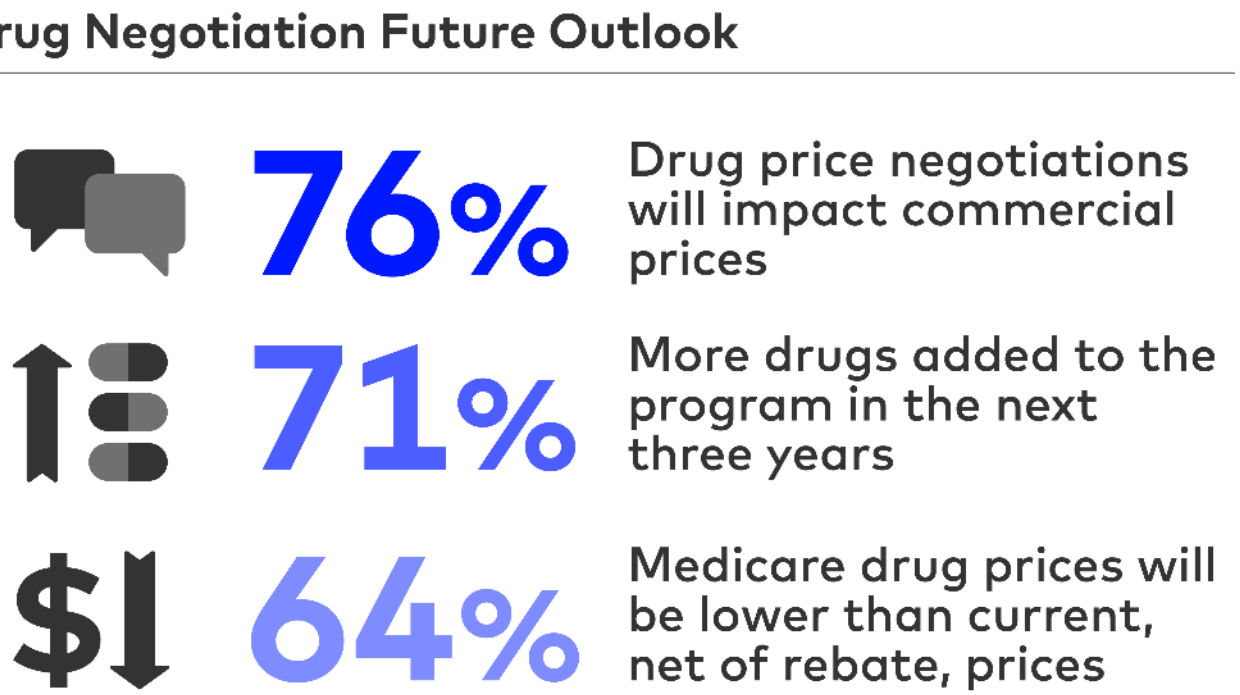
While pharma will advertise anywhere and everywhere to drive up demand, and GLP-1s will continue their meteoric rise, intensifying cost concerns will keep payors/employers scrambling. This will, in turn, spur efforts for lower cost options, including compounding pharmacies. If Medicaid spending on GLP-1s surpasses 10%, it will be difficult for states to pay, leading to additional give and take between payors and pharma.





Source: https://hcprognosis2024.venrock.com/

Venrock: Respondents Concerned on Drug Prices



For years we've asked about efforts to lower the price of drugs in the U.S. and consensus has always been that nothing would happen. A stark difference this year… not only for lower Medicare prices, but also a reset of pricing paradigms across the commercial landscape. Drug price negotiations will be a broader policy victory than expected if this is the case, but your authors are skeptical that actual prices will end up lower than current net.

Source: https://hcprognosis2024.venrock.com/

The World is Relying on the United States to Get Value-Based Drug Pricing Right

By Jason Shafrin, Louis Garrison, and Melanie D. Whittington, Opinion, *Stat+*, May 6, 2024

The changing landscape of drug pricing policy in the U.S. has implications for the global pace and direction of innovation. Drug policy changes are being influenced by perceptions of the value of novel medicines relative to their budgetary impacts, with some believing that many medicines may not be worth their cost, creating an important role for health technology assessments (HTA). The goals of these assessments are to ensure that society does not overpay for new medications, but also does not inadvertently discourage the development of worthwhile medicines and other health technologies.

For years, the U.S. was apparently content to allow market-based pricing for patent-defined periods of time to drive investment on medicines and incentivize innovation, regardless of pricing in other countries. The U.S. incentivized global biomedical innovation with its willingness to pay more for medicines, while other countries assumed perhaps they could count on getting those medicines at a discount either before or after they went generic. U.S. payers — commercial insurers, employers, and government—have often paid for medicines that other countries said were not cost-effective.

Health-technology assessment and value-based pricing (linking drug prices to the health and broader society benefits they bring) have been embraced by many countries around the world. However, many agencies or organizations that conduct HTAs, such as the Institute for Clinical and Economic Review (ICER) in the U.S., the National Institute for Health and Care Excellence (NICE) in the U.K., and the Drug Agency in Canada, focus on health benefits and health system costs from payers' perspectives, and either do not include other benefits and costs to society or take a narrow societal perspective.

Value should be measured as the total societal value, but this rarely happens. NICE uses a payer perspective — rather than a societal perspective — and sets a value per quality-adjusted life year (QALY) at around £30,000 ($38,000). That is far below the $100,000 or $150,000 QALY valuation more commonly used in the U.S. and reflects the fact that the U.K.'s National Health Service is a budget-constrained health system. NICE's narrow, payer-based approach to drug pricing has only a modest impact on the global innovation ecosystem. The U.K. makes up only 2.3% of global pharmaceutical sales, so changes in drug prices there may not materially affect drug company research and development (R&D) investment decisions. In contrast, the U.S. makes up 43% of global pharmaceutical sales, so any changes in U.S. drug pricing policy will have a large impact on R&D decisions and the number of drugs that come to the global market. In short, while U.K. drug pricing may matter a lot in the U.K., U.S. drug pricing policy matters around the globe.

Value-based drug prices should be judged in the context of all societal costs and benefits for patients today and potential patients tomorrow. While there have been earlier initiatives to quantify broader societal value — such as the ISPOR Value Flower and the Second Panel on Cost-Effectiveness in Health and Medicine — in practice, only about one quarter of published cost-effectiveness studies take any societal perspective at all.

Source: https://www.statnews.com/2024/05/06/united-states-value-based-drug-pricing

Medicare Fund's Outlook Improves on Stronger Economy, But Long-term Challenges Persist

Nathaniel Weixel, *The Hill*, May 6, 2024 (excerpt)

The financial outlook for Medicare improved in the past year, and the program's funding to pay all the costs for hospital services of older and disabled beneficiaries won't run out until 2036, five years later than last year's estimated date.

A stronger than expected economy and lower expenditures on services such as inpatient hospital and home health led to the unexpected good news for Medicare. The report also credited a policy change that lowered Medicare Advantage spending.

Just two years ago, the trust fund was projected to be depleted as early as 2028.

Once the program's reserves are depleted, it would only be able to cover 89 percent of scheduled benefits, according to the annual report from Social Security and Medicare trustees released Monday.

"We are committed to steps that would protect and strengthen these programs that Americans rely on for a secure retirement," Treasury Secretary Janet Yellen said in a statement.

In 2023, income to the hospital trust fund exceeded expenditures by $12.2 billion. The Trustees projected that surpluses would continue through 2029, followed by deficits thereafter until the trust fund becomes depleted in 2036.

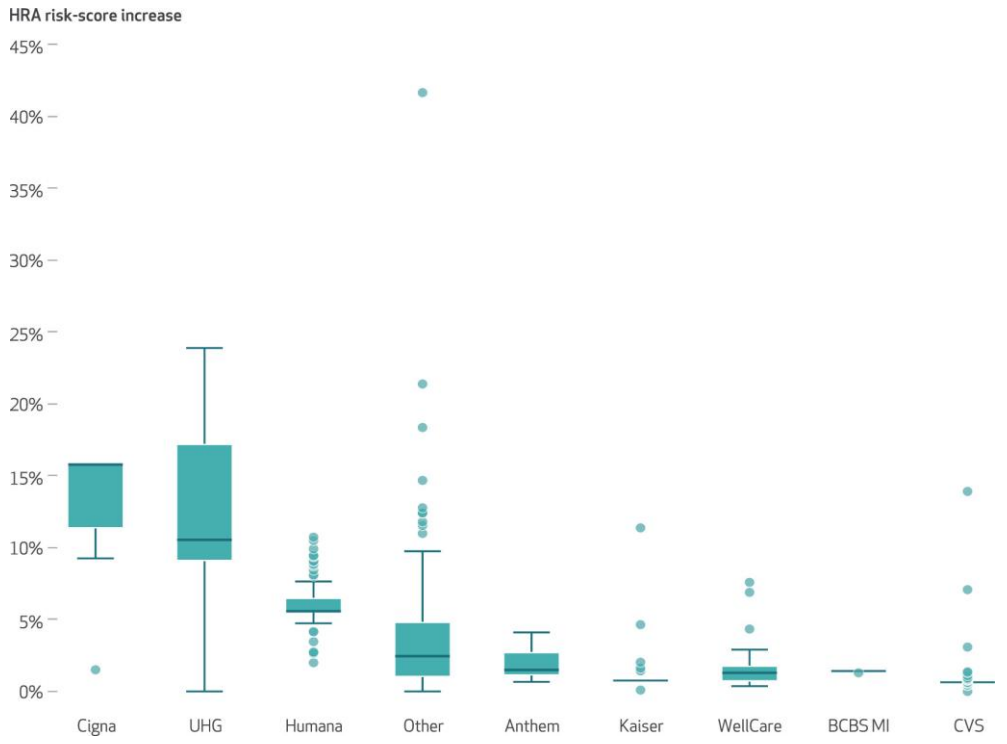
Despite the short-term good news, Medicare's costs will have to be addressed by Congress at some point. Medicare provided health insurance coverage to more than 66 million people in 2023, and the program's spending is going to continue to rise.

Source: https://thehill.com/policy/healthcare/4647137-medicare-fund-economy-solvent-yellen/

Medicare Advantage Insurers Effective at Using Health Risk Assessments to Increase Coding Intensity

Hannah O. James, Beth A. Dana, Momotazur Rahman, Daeho Kim, Amal N. Trivedi, Cyrus M. Kosar, and David J. Meyers, "Medicare Advantage Health Risk Assessments Contribute Up To $12 Billion Per Year To Risk-Adjusted Payments," *Health Affairs*, May 2024 (abstract)

With Medicare Advantage (MA) enrollment surpassing 50 percent of Medicare beneficiaries, accurate risk-adjusted plan payment rates are essential. However, artificially exaggerated coding intensity, where plans seek to enhance measured health risk through the addition or inflation of diagnoses, may threaten payment rate integrity. One factor that may play a role in escalating coding intensity is health risk assessments (HRAs)—typically in-home reviews of enrollees' health status—that enable plans to capture information about their enrollees. In this study, we evaluated the impact of HRAs on Hierarchical Condition Categories (HCC) risk scores, variation in this impact across contracts, and the aggregate payment impact of HRAs, using 2019 MA encounter data. We found that 44.4 percent of MA beneficiaries had at least one HRA. Among those with at least one HRA, HCC scores increased by 12.8 percent, on average, as a result of HRAs. More than one in five enrollees had at least one additional HRA-captured diagnosis, which raised their HCC score. Potential scenarios restricting the risk-score impact of HRAs correspond with $4.5–$12.3 billion in reduced Medicare spending in 2020. Addressing increased coding intensity due to HRAs will improve the value of Medicare spending and ensure appropriate payment in the MA program.



Source: https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2023.00787

Medicare Prior Authorization Bill Moving in Senate

Suzanne Blake, "Medicare Advantage to Be Radically Changed Under New Plan," *Newsweek*, May 10, 2024 (excerpt)

And in many cases, seniors on Medicare Advantage have to get prior authorization approval to access the treatments they need. All that would change if Democratic Rhode Island Senator Sheldon Whitehouse's plan gets passed.

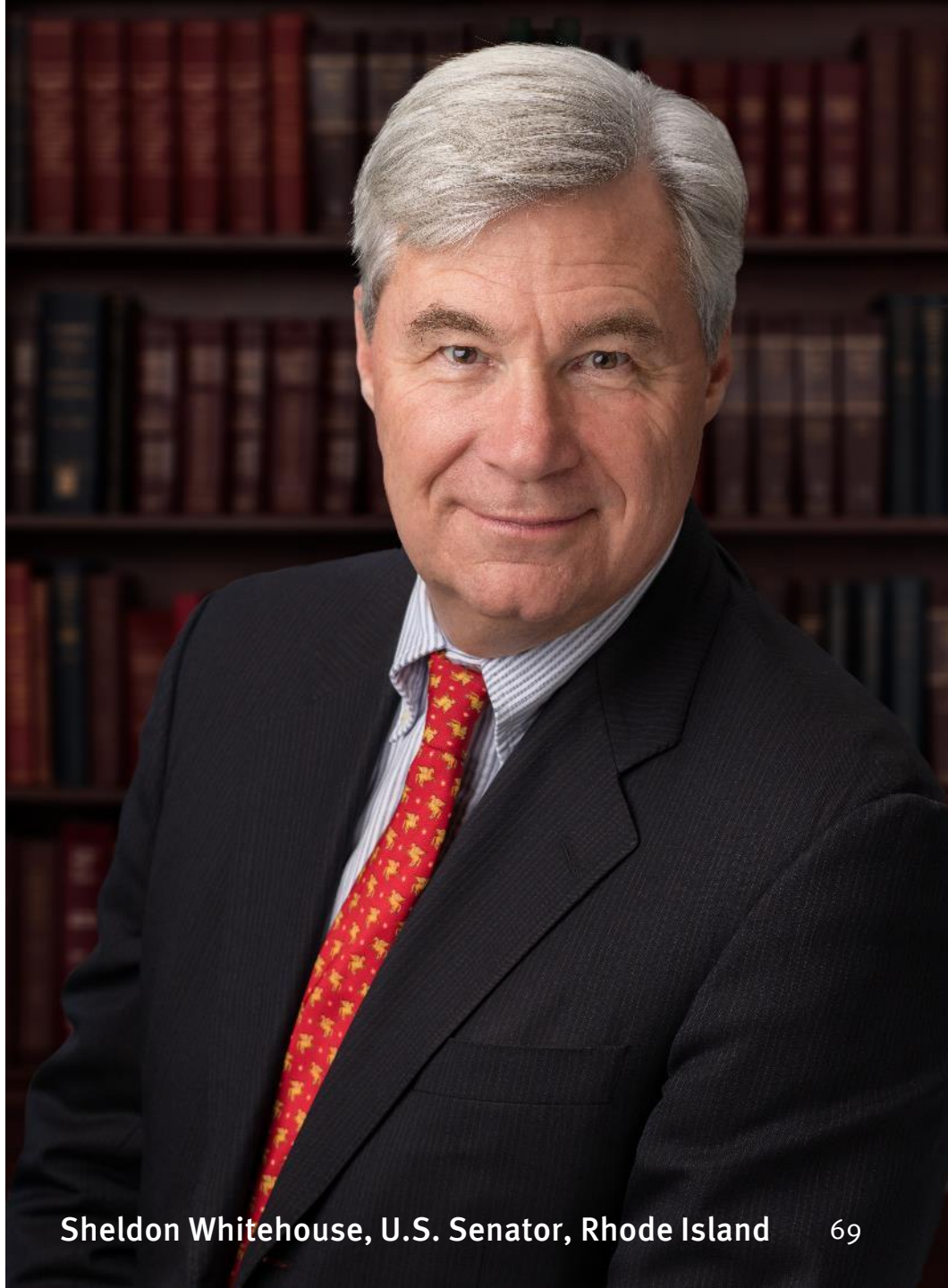
Whitehouse argues that insurers with prior authorization requirements on doctors in accountable care organizations should need their own prior approval from the Centers for Medicare and Medicaid Services.

"There is no logic to prior authorization," Whitehouse, who serves as the chairman of the Senate Budget Committee, said at a committee hearing this week. "So I propose the companies in Medicare get prior authorization from CMS before they're allowed to impose prior authorization on doctors who are practicing in successful accountable care organizations that have a proven track record of providing efficient patient care. No prior authorization without prior authorization."

Whitehouse also said that billing and insurance-related costs total nearly $200 billion yearly, and the lack of standardization has healthcare costs piling up.

If there were fewer prior authorizations, healthcare workers would likely benefit as well. Many sought out streamlined paperwork and more simplified billing forms in an HHS Surgeon General 2022 Health Worker Burnout report.

Source: https://www.newsweek.com/medicare-advantage-radically-changed-new-plan-1899395



Sheldon Whitehouse, U.S. Senator, Rhode Island

One in Eight Americans Have Tried a GLP-1 Drug

Alex Montero, Grace Sparks, Marley Presiado, and Liz Hamel, Kaiser Family Foundation, May 10, 2024

The latest KFF Health Tracking Poll finds that about one in eight adults (12%) say they have ever taken a GLP-1 agonist – an increasingly popular class of prescription drugs used for weight loss and to treat diabetes or prevent heart attacks or strokes for adults with heart disease – including 6% who say they are currently taking such a drug.

The share who report ever taking these drugs rises to four in ten (43%) among adults who have been told by a doctor that they have diabetes, a quarter who have been told they have heart disease, and one in five (22%) who have been told by a doctor that they are overweight or obese in the past five years1. Public awareness of GLP-1 drugs has increased in the past year, with about one-third (32%) of adults now saying they have heard “a lot” about these drugs, up from 19% in July 2023.

Most adults who have taken GLP-1 drugs say they took them to treat a chronic condition including diabetes or heart disease (62%), while about four in ten say they took them primarily to lose weight.

About half (54%) of all adults who have taken GLP-1 drugs say it was difficult to afford the cost, including one in five (22%) who say it was “very difficult.” While most insured adults who have taken these drugs say their insurance covered at least part of the cost, even among insured adults about half (53%) say the cost was difficult to afford.

While 8% of adults ages 65 and older say they have taken a GLP-1 medication for a chronic condition, just 1% say they have ever taken a GLP-1 drug to lose weight, which may reflect Medicare’s lack of coverage for prescription drugs used for weight loss. Nearly four in ten (37%) adults ages 65 and older report being told by a doctor they are overweight or obese in the past five years.

With Medicare currently prohibited by law from covering prescription drugs used for weight loss, six in ten adults say they think Medicare should cover the cost of these drugs when prescribed for weight loss for people who are overweight, including more than half of Democrats, independents and Republicans.

Source: https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-may-2024-the-publics-use-and-views-of-glp-1-drugs/

BCG Analysis Shows that AI Discovered Drugs Are Doing Better in Early Clinical Trials

June 2024

How successful are AI-discovered drugs in clinical trials? A first analysis and emerging lessons

Madura KP Jayatunga [1], Margaret Ayers [1], Lotte Bruens [2], Dhruv Jayanth [3], Christoph Meier [1,*]

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AI techniques are making inroads into the field of drug discovery. As a result, a growing number of drugs and vaccines have been discovered using AI. However, questions remain about the success of these molecules in clinical trials. To address these questions, we conducted a first analysis of the clinical pipelines of AI-native Biotech companies. In Phase I we find AI-discovered molecules have an 80–90% success rate, substantially higher than historic industry averages. This suggests, we argue, that AI is highly capable of designing or identifying molecules with drug-like properties. In Phase II the success rate is ~40%, albeit on a limited sample size, comparable to historic industry averages. Our findings highlight early signs of the clinical potential of AI-discovered molecules.

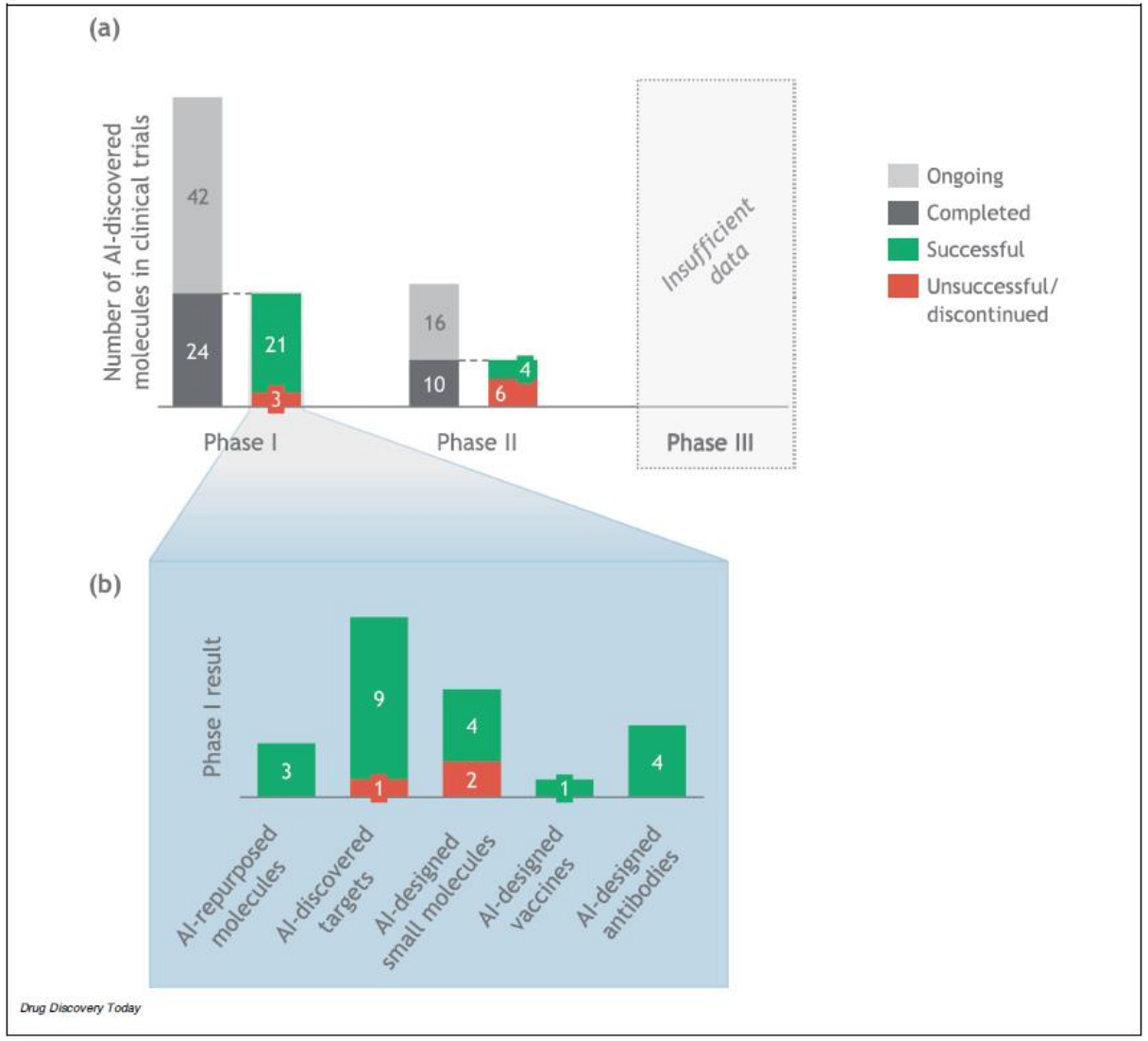


FIGURE 2
The success of AI-discovered molecules in clinical trials so far. The analysis includes molecules that were partnered with pharmaceutical companies and excludes COVID-19-related molecules. **(a)** Clinical success of AI-discovered molecules by clinical Phase. **(b)** AI-discovered molecules that have completed Phase I trial, by mode-of-discovery.

Source: https://www.sciencedirect.com/science/article/pii/S135964462400134X

ASGCT Conference: There is Still a Long Way to Go in Cell and Gene Therapy

Greg Slabodkin, *Biospace*, May 10, 2024 (excerpt)

The 2024 American Society of Gene & Cell Therapy annual meeting attracted a record number of attendees and abstracts, testimony to the tremendous growth of the cell and gene therapy industry. But for me, my week onsite in Baltimore laid bare the major challenges that stand between cell and gene therapies (CGTs) and the masses.

To be sure, the CGT space has come a long way in a very short time, with a record seven approvals in 2023, and this year looking to bring even more therapies to market. The commercial side of this space is particularly apparent now as the race between Vertex Pharmaceuticals' CRISPR-based Casgevy and bluebird bio's gene therapy Lyfgenia heats up. And there were some amazing technologies in the spotlight at ASGCT 2024, with several major advancements poised to transform the sector. Particularly noteworthy were new advancements in gene editing. While the CRISPR genome editing platform earned the Nobel Prize in 2020, the technology has limitations and risks, and researchers are looking to develop more accurate and safe DNA editors.

Another leap in the CGT space is in engineered cell therapies, which seem to be entering a second revolution, the first being the commercialization of CAR-T cell therapies. However, Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, provided a sobering assessment at ASGCT 2024 of the opportunities and challenges facing the industry. Marks said that it's "quite an exciting time" for gene therapies in the U.S. with 20 indications and 19 products approved but emphasized there are "some real challenges" including manufacturing, clinical development timelines and different global regulatory requirements.

"We are at a critical juncture," Marks, the FDA's top biologics regulator, said. "We see products dropping out of development because they're simply not felt to be commercially viable," particularly for rare diseases.

ASGCT 2024 fostered a lot of good conversations about the regulatory hurdles facing the CGT industry. However, just as important were the discussions around the significant manufacturing challenges confronting the sector.

Source: https://www.biospace.com/article/cell-and-gene-therapies-still-have-long-way-to-go-in-fulfilling-promise/

Freeline Reports Stunning Data on Gaucher's at ASGCT

LONDON, May 09, 2024 (GLOBE NEWSWIRE) Freeline Therapeutics today announced new clinical data from its ongoing Phase 1/2 GALILEO-1 trial of FLT201, its adeno-associated virus (AAV) gene therapy candidate for Gaucher disease, showing substantial reductions in glucosylsphinogsine (lyso-Gb1), one of the best predictors of clinical response, in patients with persistently high levels despite years of treatment with currently approved therapies, as well as early signs of clinical improvements in bone marrow burden and fatigue. FLT201 continues to demonstrate a favorable safety and tolerability profile.

Gaucher disease is caused by a mutation in the GBA1 gene, which leads to a deficiency of the glucocerebrosidase (GCase) enzyme. As a result, substrates build up in cells and organs throughout the body, causing symptoms including enlarged spleen and liver, low blood counts, bone pain, fatigue and reduced lung function. FLT201 delivers a rationally engineered version of the GCase enzyme (GCase85) with greater stability than wildtype GCase, designed to stay in cells longer to more effectively clear substrates and penetrate difficult-to-reach tissues, including bone, that currently approved therapies poorly address. Reductions in lyso-Gb1 levels in the blood are highly correlated with substrate reduction in disease-affected tissues and positive clinical outcomes in Gaucher disease.

"Gaucher disease, the most common lysosomal storage disorder, is severe and progressive when not treated. Currently approved treatments have made a significant difference for people with Gaucher disease, but there is not an existing cure. Patients require life-long treatment and many continue to experience symptoms, including enlarged organs, chronic bone pain and fatigue," said Ozlem Goker-Alpan, M.D., founder and CEO of the Lysosomal and Rare Disorder Research and Treatment Center (LDRTC) and an investigator in the Phase 1/2 GALILEO-1 trial of FLT201. "A gene therapy that could deliver the same or better efficacy than currently available treatments, while freeing people from an ongoing treatment burden, would mark a significant advance in the treatment paradigm for Gaucher disease. I am very encouraged by the clinical data to date for FLT201."

The data demonstrated:

1. Favorable safety and tolerability, with no infusion reactions and no serious adverse events. Modest alanine-transaminase (ALT) elevations in some patients were managed with immune therapy, with no impact to efficacy. Non-serious adverse events were all mild or moderate in severity.
2. Robust and continuous expression in plasma GCase, with clear evidence of cellular uptake of GCase from the plasma as measured by GCase activity in the leukocytes. Leukocytes are established indicators for broad cellular uptake in Gaucher disease.
3. Substantial reductions in lyso-Gb1 in patients who entered the trial with persistently high lyso-Gb1 levels despite years on prior treatment with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). Low lyso-Gb1 levels were maintained in one patient who entered the trial with well-controlled levels.
4. Maintenance of hemoglobin levels, an established endpoint for Gaucher disease clinical trials, was observed post withdrawal of treatment with ERT or SRT. Improvement or maintenance of platelet counts was also seen post withdrawal of treatment with ERT or SRT.
5. Reductions in bone marrow burden in the first four patients as of 12 to 38 weeks post-dosing, indicating clearance of substrate from the bone marrow and reappearance of healthy, fatty marrow.

Source: https://freeline.life/freeline-presents-positive-new-data-from-phase-1-2-trial-of-flt201-its-novel-gene-therapy-candidate-for-gaucher-disease-in-late-breaking-oral-presentation-at-asgct-27th-annual-meeting-2/

Regeneron's Gene Therapy Triumphs Twice, Restoring Hearing in Children

Phalguni Deswal, *Clinical Trials Arena*, May 9, 2024 (excerpt)

Regeneron Pharmaceuticals' gene therapy for otoferlin hearing loss, DB-OTO, has restored hearing to normal in an 11-month-old child within 24 weeks and improved hearing in another four-year-old child at six weeks.

The data is from an open-label Phase I/II CHORD trial (NCT05788536), which was presented at the 2024 American Society of Gene and Cell Therapy (ASGCT) annual conference taking place in Baltimore from 7 to 11 May.

As part of the CHORD study, both children received a single intracochlear injection of DB-OTO in one ear. The trial's secondary endpoints include hearing improvement, measured using auditory brainstem response (ABR) and behavioural audiometry with pure-tone audiometry (PTA).

At 24 weeks, the younger child observed improvement of hearing to normal levels, with an average 80 decibels (dB) improvement from baseline. The second participant observed an average 16dB improvement in hearing response, compared to baseline, at six weeks. The surgical procedure and the gene therapy were well tolerated, with no treatment-related adverse events or serious adverse events.

DB-OTO is an adeno-associated virus gene therapy designed to restore hearing in patients with congenital otoferlin hearing loss. The rare hearing loss is caused by variants in the otoferlin gene that impair the production of the OTOF protein, responsible for communication between the sensory cells of the inner ear and the auditory nerve.

Other companies developing gene therapies for improving otoferlin hearing loss include Sensorion and Akouos. In January, Sensorion received the go-ahead to start Phase I/II clinical trial of its gene therapy SENS-501 for otoferlin hearing loss in select European countries. The study will evaluate SENS-501 in children aged six to 31 months at the time of treatment.

Source: https://www.clinicaltrialsarena.com/news/regenerons-gene-therapy-triumphs-twice-restoring-hearing-in-children/

Solving the Cancer Mystery That Devastated My Family

For decades, Lawrence Ingrassia wondered why so many of his loved ones got cancer. Then a team of dedicated researchers discovered the gene p53.

Lawrence Ingrassia, WSJ, May 10, 2024 (excerpt)

There would be, alas, much more to say. Cancer was far from done with my family. My sister Angela was diagnosed with abdominal cancer at age 23 in 1980; my nephew Charlie developed the first of several cancers, a soft-tissue tumor in his cheek, at age 2 in 1982; my sister Gina got lung cancer at age 32 in 1987; and my brother Paul would develop multiple cancers, starting with lung cancer at age 46 in 1997.

It would take decades of research by doctors to solve the mystery of what was behind all these cancers. While we couldn't have known at the time, the long search that led to an answer began while my mother was still battling cancer.

In the summer of 1967, a 27-year-old doctor named Frederick P. Li accepted a job at the National Cancer Institute's epidemiology department. The mission of the department, a fledgling group of about a half-dozen researchers, was to examine patterns of disease that might provide clues about susceptibility and early detection. In truth, epidemiology was a backwater at the NCI. The prestigious jobs were held by doctors concocting experimental therapies or researchers studying the causes of cancer, especially viral causes, which were then considered the leading suspect for most tumors.

The latest tragedy convinced Li and Fraumeni to continue their research. Little did they know how long it would take. Over two decades, they painstakingly tracked a growing number of other cancer-prone families. Mounting evidence, and an increased understanding of genetics, pointed to heredity as the cause, but a definitive answer proved elusive.

Then, in late 1990, came a breakthrough. Using new gene-sequencing technology on the tissue that Li and Fraumeni had presciently collected from affected family members, researchers identified a very rare inherited mutation in a gene that was unknown when they began their research. Known commonly as p53, it is a tumor suppressor gene with the power to block potentially cancerous cells from becoming malignant.

But when mutated, p53 loses its cancer-fighting ability, dramatically increasing the chances of cancer. It has since become the most studied gene in the human body, so important that it has been dubbed the "guardian of the genome." The mutation is so pernicious that 50% of people who inherit it develop cancer by age 40, versus about 5% for the overall population. More than 90% of people with the mutation get cancer in their lifetime.

The breakthrough was major news, not just in scientific publications but in The Wall Street Journal and New York Times as well. It advanced the understanding of all cancers and would lead to improved treatments. Researchers have since found that extensive screening of patients with the inherited p53 mutation, including full-body MRI scans and other tests, can prolong their lives by detecting early-stage tumors. But there is no way to prevent recurrences or new cancers, as no cure has been found for what is now known as Li-Fraumeni Syndrome.

By the time of the researchers' groundbreaking discovery, my two sisters had died, both within about six months of being diagnosed with cancer in the 1980s. Still, despite the media attention to the p53 finding—and the fact that my brother Paul and I were both editors at The Wall Street Journal—the rare mutation's role in some cancer-prone families escaped our attention. We long had surmised the cancers were environmental. Our dad worked as a research chemist, and we concluded that he must have brought home carcinogens on his clothes that, after being breathed in, led years later to cancer.

Source: https://www.wsj.com/health/solving-the-cancer-mystery-that-devastated-my-family-dd5e6e53

History of Li-Fraumeni Syndrome (LFS) and the LFS Association

Founding Fathers

1969

Two NIH scientists, Drs. Frederick Li and Joseph Fraumeni, report a rare familial syndrome of multiple cancers in children and young adults, including sarcomas, breast cancer and other tumors. This discovery of childhood tumors and cancer-prone families occurs at a time when little attention was given to the role of genetic susceptibility in cancer.

1979

Drs. David Lane and Arnold Levine co-discover the *TP53* tumor suppressor gene, which, over time, is recognized to be the cause of a wide range of cancers. *TP53* is currently one of the most studied genes in the world.

1982

Researchers in the United Kingdom are the first to coin the name "Li-Fraumeni syndrome."

1988

Drs. Judy Garber, Li, Fraumeni and colleagues document the elevated risk of subsequent cancers in 24 families with LFS, note the especially high risk for breast cancer in young women, and propose the first "classical" definition of LFS based on clinical and familial criteria. Drs. Louise Strong in Houston, Jillian Birch in Manchester, and Ros Eeles in London provide important insights into the LFS component tumors and mode of inheritance.

1990

A multi-institutional team led by Drs. David Malkin and Stephen Friend in Boston discover that *inherited* ("germline") mutations of *TP53* are the primary cause of LFS. This opens the door for predictive and diagnostic genetic testing.

1992

Recommendations that address clinical, psychosocial, ethical, economic and legal ramifications of genetic testing in LFS with applications to other genetic disorders, particularly in children, are published.

1992

A team lead by Drs. Alan Balmain and Larry Donehower in Houston create the first p53-deficient mouse. It has a very high incidence of cancer that are subsequently shown to occur earlier when the mice are exposed to radiation.

1998

A team led by Drs. Li and Fraumeni document the elevated risk of subsequent cancers in LFS patients, even outside the radiation field of a primary malignancy.

2001

A collaboration of investigators in Brazil and Memphis describe a unique germline *TP53* mutation in children with adrenal cortical cancer in southeastern Brazil.

2004

Teams led by Drs. Gigi Lozano in Houston and Tyler Jacks in Boston describe the first *TP53* mutant mouse models of LFS, which are subsequently used to better understand how cancers develop and progress.

2007

Dr. Maria Isabel Achatz provides evidence that the 'Brazilian' *TP53* mutation is a "founder mutation" derived from a common ancestor migrating long ago from Portugal. The spectrum of cancers in these families resembles those with "classic" LFS.

2010

NIH convenes a meeting of LFS researchers and, for the first time, LFS patients and family members, to generate plans for an international and multidisciplinary alliance of scientists, clinicians, psychologists and genetic counselors - the Li-Fraumeni Exploratory (LiFE) Consortium. At this meeting, families form the LFS Association (LFSA) to partner with LiFE and best meet the needs of the LFS patient community.

2011

Dr. Malkin and colleagues at the Hospital for Sick Children in Toronto develop screening recommendations for early cancer detection in carriers of the defective *TP53*. The "Toronto protocol" provides a comprehensive program of clinical, biochemical and imaging, including whole-body MRIs.

2015

Researchers in France, led by Drs. Thierry Frebourg and Laurence Brugieres, update the "Chompret criteria" further refining the clinical and familial characteristics widely used to help identify potential carriers and facilitate the diagnosis of LFS.

2016

The LFSA Medical Advisory Board is formed, followed shortly thereafter with the formation of the LFSA Genetic Counseling Advisory Group.

2017

New screening recommendations are published based on the modification of the "Toronto protocol." Comprehensive consideration is given to the impact on patients to maximize participation in early tumor detection screening.

2017

The LFS Association pilots its first Youth Workshop with teenage participants from around the world, and launches international chapters in Germany, Saudi Arabia, and the Netherlands, in addition to Canada, Australia/New Zealand, and Brazil.

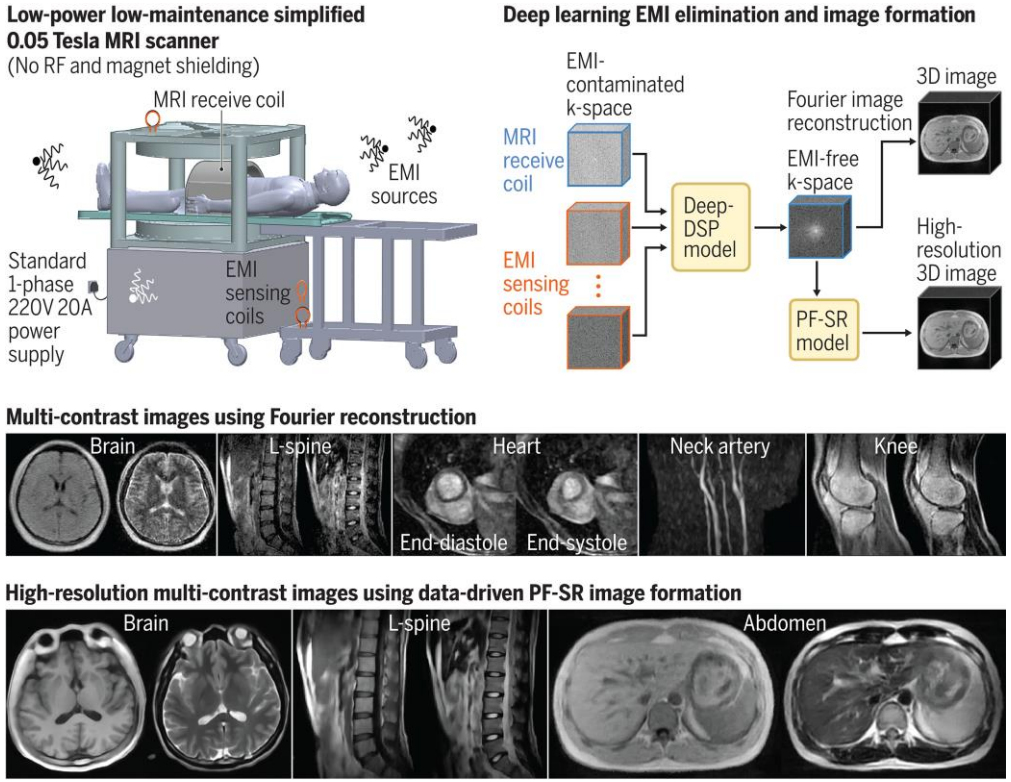
Source: https://www.lfsassociation.org/50-years-of-lfs/

Whole-Body MRI at 0.05 Tesla

Zhao Y, Ding Y, Lau V, Man C, Su S, Xiao L, Leong ATL, Wu EX, "Whole-body magnetic resonance imaging at 0.05 Tesla," *Science*, May 10, 2024

We developed a highly simplified whole-body ultra-low-field (ULF) MRI scanner that operates on a standard wall power outlet without RF or magnetic shielding cages. This scanner uses a compact 0.05 Tesla permanent magnet and incorporates active sensing and deep learning to address electromagnetic interference (EMI) signals. We deployed EMI sensing coils positioned around the scanner and implemented a deep learning method to directly predict EMI-free nuclear magnetic resonance signals from acquired data. To enhance image quality and reduce scan time, we also developed a data-driven deep learning image formation method, which integrates image reconstruction and three-dimensional (3D) multiscale super-resolution and leverages the homogeneous human anatomy and image contrasts available in large-scale, high-field, high-resolution MRI data.

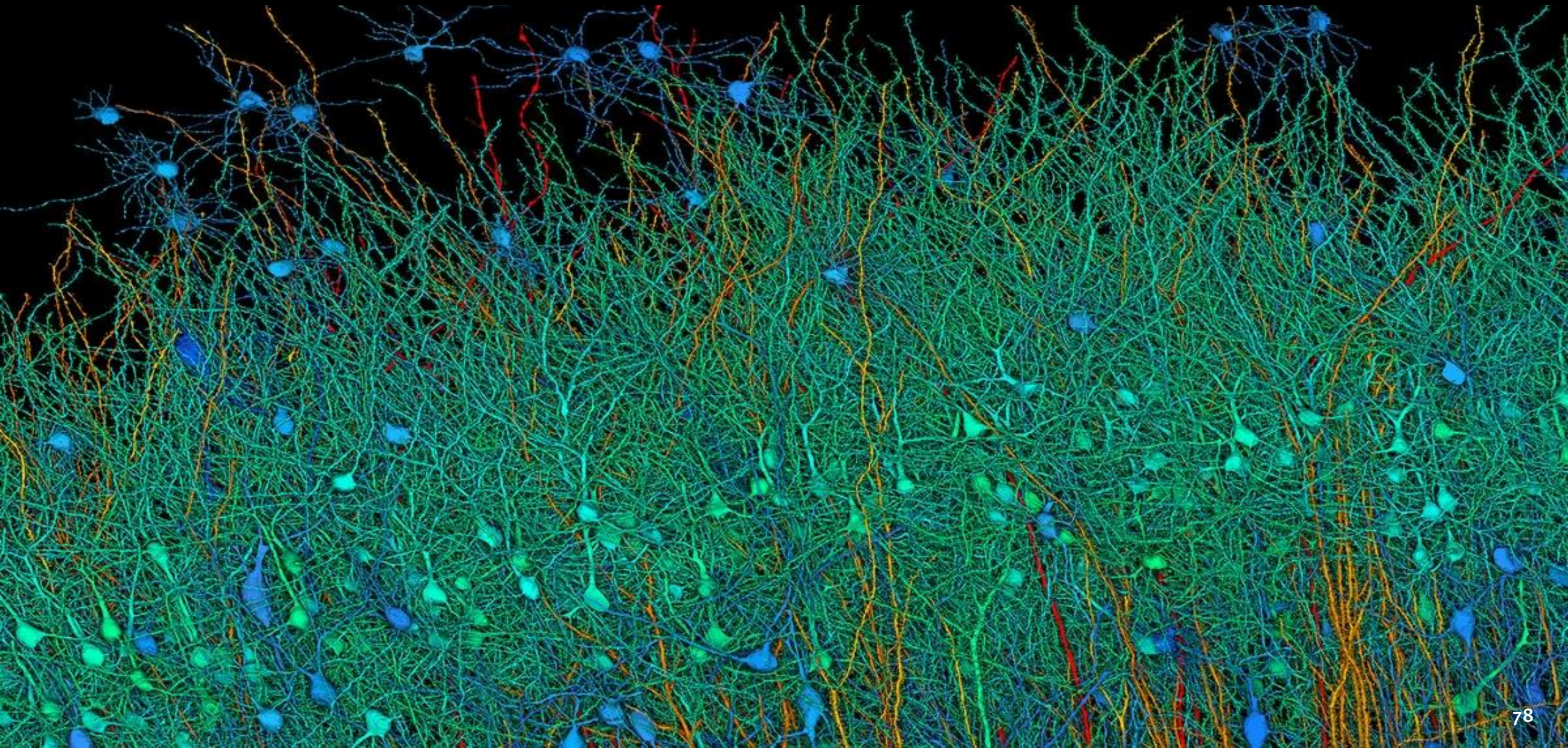
We implemented commonly used clinical protocols at 0.05 Tesla, including T1-weighted, T2-weighted, and diffusion-weighted imaging, and optimized their contrasts for different anatomical structures. Each protocol was designed to have a scan time of 8 minutes or less with an image resolution of approximately 2×2×8 mm^3. The scanner power consumption during scanning was under 1800W and around 300W when idle. We conducted imaging on healthy volunteers, capturing brain, spine, abdomen, lung, musculoskeletal, and cardiac images. Deep learning signal prediction effectively eliminated EMI signals, enabling clear imaging without shielding. The brain images showed various brain tissues whereas the spine images revealed intervertebral disks, spinal cord, and cerebrospinal fluid. Abdominal images displayed major structures like the liver, kidneys, and spleen. Lung images showed pulmonary vessels and parenchyma. Knee images identified knee structures such as cartilage and meniscus. Cardiac cine images depicted the left ventricle contraction and neck angiography revealed carotid arteries. Furthermore, deep learning image formation greatly improved the 0.05 Tesla image quality for various anatomical structures, including the brain, spine, abdomen, and knee; it also effectively suppressed noise and artifacts and increased image spatial resolution.



Computing-powered whole-body MRI at 0.05 Tesla.
(Top) Prototype of a low-cost, low-power, compact, and shielding-free imaging system using an open 0.05 Tesla permanent magnet. It incorporates active sensing and deep learning to address EMI signals. (Middle) Typical images of various anatomical structures using conventional image reconstruction. (Bottom) High-resolution images using deep learning image formation by harnessing large-scale high-field MRI data.

Source: https://www.science.org/doi/10.1126/science.adm7168

Lichtman Lab at Harvard Maps the Human Brain



Cubic Millimeter of Brain Mapped in Spectacular Detail

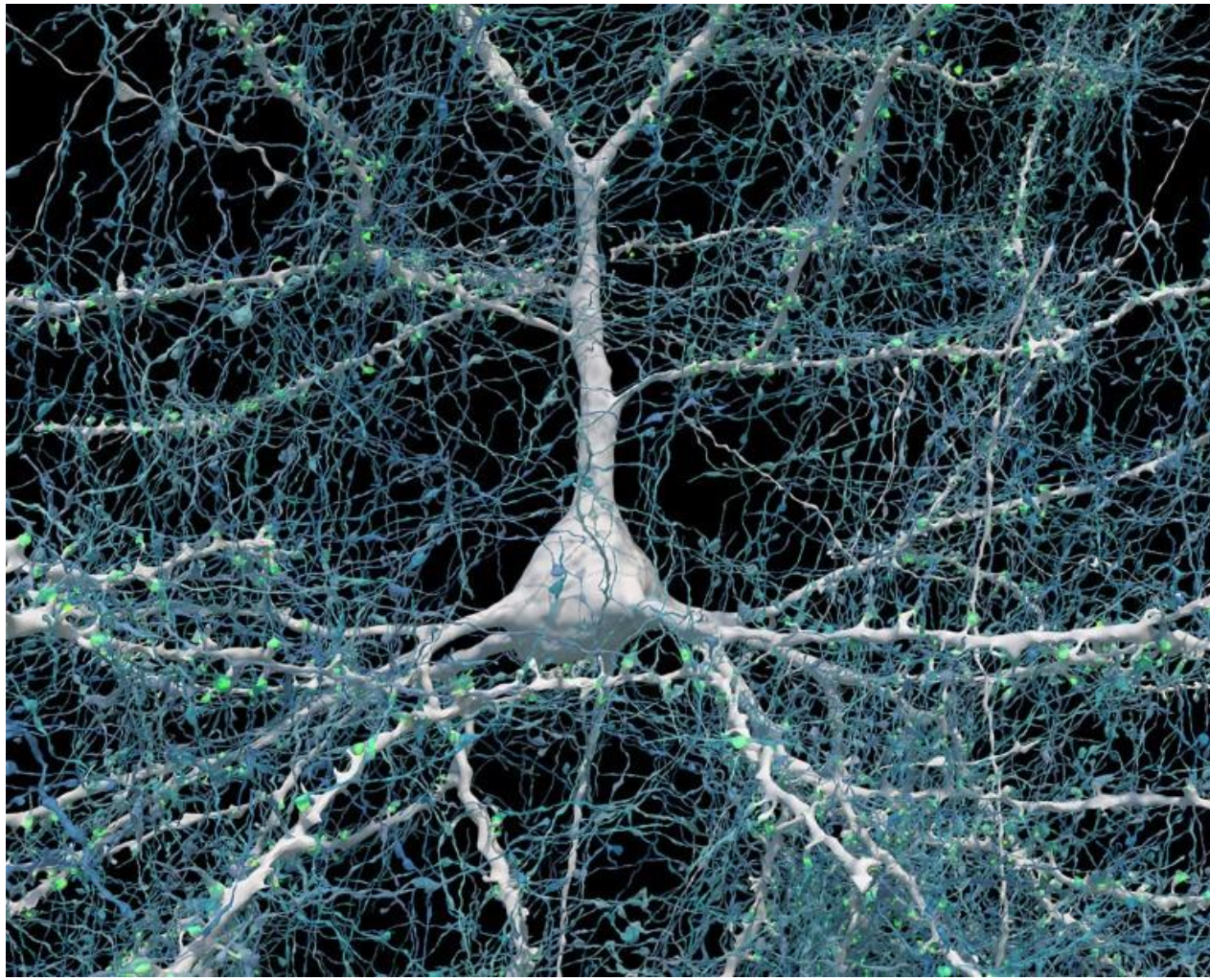
Carissa Wong, *Nature*, May 9,. 2024 (excerpt)

Researchers have mapped a tiny piece of the human brain in astonishing detail. The resulting cell atlas, which was described today in Science and is available online, reveals new patterns of connections between brain cells called neurons, as well as cells that wrap around themselves to form knots, and pairs of neurons that are almost mirror images of each other.

The 3D map covers a volume of about one cubic millimetre, one-millionth of a whole brain, and contains roughly 57,000 cells and 150 million synapses — the connections between neurons. It incorporates a colossal 1.4 petabytes of data. “It’s a little bit humbling,” says Viren Jain, a neuroscientist at Google in Mountain View, California, and a co-author of the paper. “How are we ever going to really come to terms with all this complexity?”

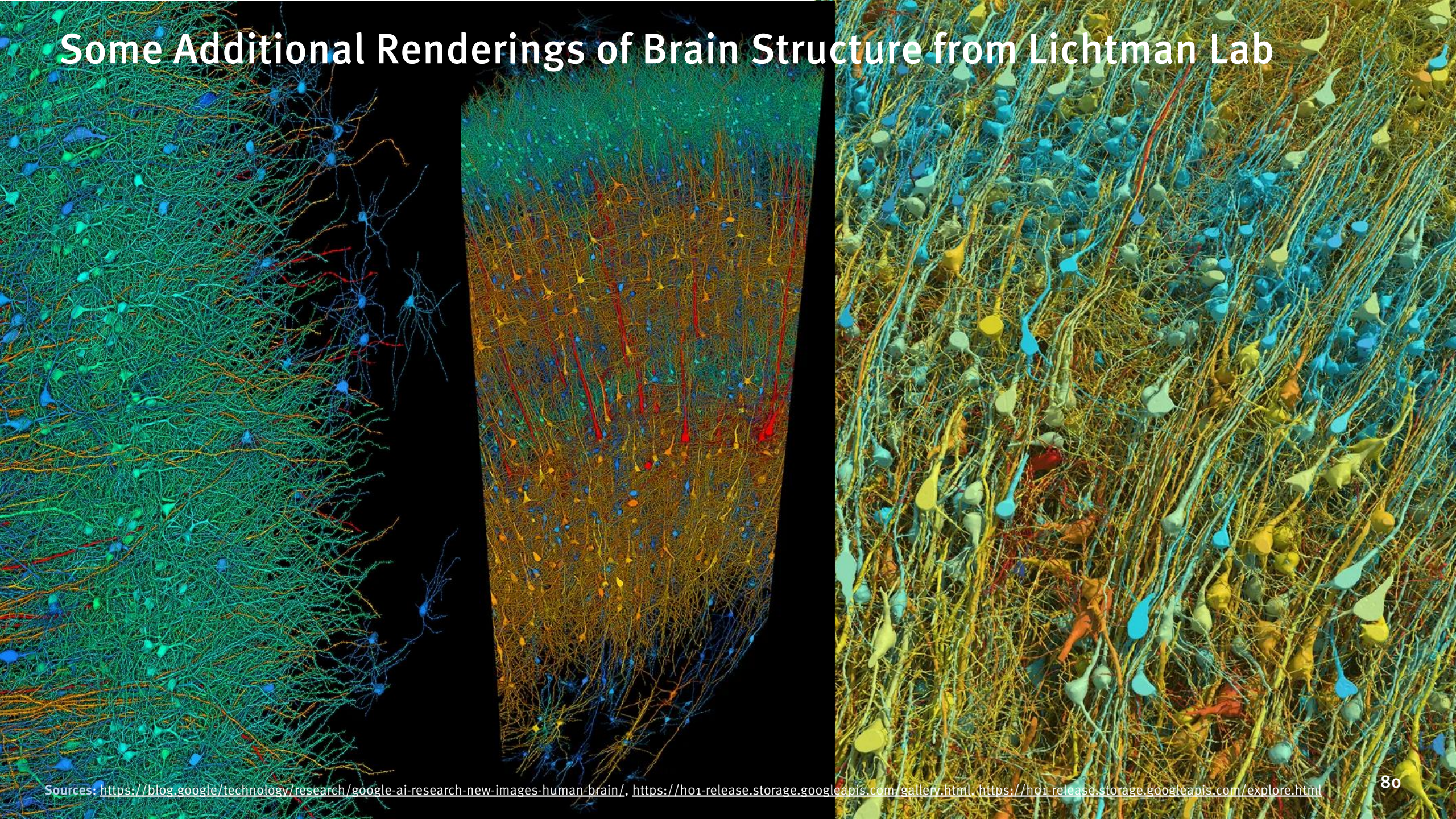
The brain fragment was taken from a 45-year-old woman when she underwent surgery to treat her epilepsy. It came from the cortex, a part of the brain involved in learning, problem-solving and processing sensory signals. The sample was immersed in preservatives and stained with heavy metals to make the cells easier to see. Neuroscientist Jeff Lichtman at Harvard University in Cambridge, Massachusetts, and his colleagues then cut the sample into around 5,000 slices — each just 34 nanometres thick — that could be imaged using electron microscopes.

Source: https://www.nature.com/articles/d41586-024-01387-9



A single neuron (white) shown with 5,600 of the axons (blue) that connect to it. The synapses that make these connections are shown in green. Credit: Google Research & Lichtman Lab (Harvard University). Renderings by D. Berger (Harvard University)

Some Additional Renderings of Brain Structure from Lichtman Lab



Sources: https://blog.google/technology/research/google-ai-research-new-images-human-brain/, https://h01-release.storage.googleapis.com/gallery.html, https://h01-release.storage.googleapis.com/explore.html

Google Helped Make an Exquisitely Detailed Map of a Tiny Piece of the Human Brain

Cassandra Willyard, *MIT Technology Review*, May 9, 2024 (excerpt)

A team led by scientists from Harvard and Google has created a 3D, nanoscale-resolution map of a single cubic millimeter of the human brain. Although the map covers just a fraction of the organ—a whole brain is a million times larger—that piece contains roughly 57,000 cells, about 230 millimeters of blood vessels, and nearly 150 million synapses. It is currently the highest-resolution picture of the human brain ever created.

To make a map this finely detailed, the team had to cut the tissue sample into 5,000 slices and scan them with a high-speed electron microscope. Then they used a machine-learning model to help electronically stitch the slices back together and label the features. The raw data set alone took up 1.4 petabytes. "It's probably the most computer-intensive work in all of neuroscience," says Michael Hawrylycz, a computational neuroscientist at the Allen Institute for Brain Science, who was not involved in the research. "There is a Herculean amount of work involved."

Many other brain atlases exist, but most provide much lower-resolution data. At the nanoscale, researchers can trace the brain's wiring one neuron at a time to the synapses, the places where they connect. "To really understand how the human brain works, how it processes information, how it stores memories, we will ultimately need a map that's at that resolution," says Viren Jain, a senior research scientist at Google and coauthor on the paper, published in Science on May 9. The data set itself and a preprint version of this paper were released in 2021.

Once the researchers had the sample, they had to carefully preserve it in resin so that it could be cut into slices, each about a thousandth the thickness of a human hair. Then they imaged the sections using a high-speed electron microscope designed specifically for this project.

Next came the computational challenge. "You have all of these wires traversing everywhere in three dimensions, making all kinds of different connections," Jain says. The team at Google used a machine-learning model to stitch the slices back together, align each one with the next, color-code the wiring, and find the connections. This is harder than it might seem. "If you make a single mistake, then all of the connections attached to that wire are now incorrect," Jain says.

The map, which is freely available at a web platform called Neuroglancer, is meant to be a resource other researchers can use to make their own discoveries. "Now anybody who's interested in studying the human cortex in this level of detail can go into the data themselves. They can proofread certain structures to make sure everything is correct, and then publish their own findings," Jain says. (The preprint has already been cited at least 136 times.)

Source: https://www.technologyreview.com/2024/05/09/1092223/google-map-cubic-millimeter-human-brain/

AlphaFold 3 and Protein Languages

AlphaFold 3 Predicts the Structure and Interactions of all of Life's Molecules

Introducing AlphaFold 3, a new AI model developed by Google DeepMind and Isomorphic Labs. By accurately predicting the structure of proteins, DNA, RNA, ligands and more, and how they interact, we hope it will transform our understanding of the biological world and drug discovery.

Inside every plant, animal and human cell are billions of molecular machines. They're made up of proteins, DNA and other molecules, but no single piece works on its own. Only by seeing how they interact together, across millions of types of combinations, can we start to truly understand life's processes.

In a paper published in Nature, we introduce AlphaFold 3, a revolutionary model that can predict the structure and interactions of all life's molecules with unprecedented accuracy. For the interactions of proteins with other molecule types we see at least a 50% improvement compared with existing prediction methods, and for some important categories of interaction we have doubled prediction accuracy.

We hope AlphaFold 3 will help transform our understanding of the biological world and drug discovery. Scientists can access the majority of its capabilities, for free, through our newly launched AlphaFold Server, an easy-to-use research tool. To build on AlphaFold 3's potential for drug design, Isomorphic Labs is already collaborating with pharmaceutical companies to apply it to real-world drug design challenges and, ultimately, develop new life-changing treatments for patients.

Our new model builds on the foundations of AlphaFold 2, which in 2020 made a fundamental breakthrough in protein structure prediction. So far, millions of researchers globally have used AlphaFold 2 to make discoveries in areas including malaria vaccines, cancer treatments and enzyme design. AlphaFold has been cited more than 20,000 times and its scientific impact recognized through many prizes, most recently the Breakthrough Prize in Life Sciences. AlphaFold 3 takes us beyond proteins to a broad spectrum of biomolecules. This leap could unlock more transformative science, from developing biorenewable materials and more resilient crops, to accelerating drug design and genomics research.

Source: https://blog.google/technology/ai/google-deepmind-isomorphic-alphafold-3-ai-model/

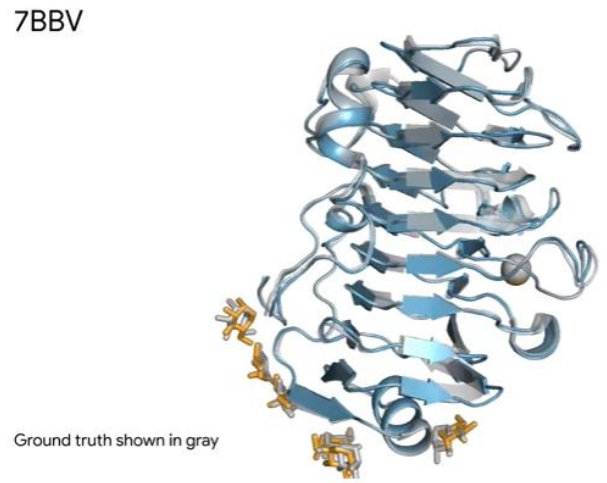
How AlphaFold 3 Reveals Life's Molecules

Google Blog, May 10, 2024

Given an input list of molecules, AlphaFold 3 generates their joint 3D structure, revealing how they all fit together. It models large biomolecules such as proteins, DNA and RNA, as well as small molecules, also known as ligands — a category encompassing many drugs. Furthermore, AlphaFold 3 can model chemical modifications to these molecules which control the healthy functioning of cells, that when disrupted can lead to disease.

AlphaFold 3's capabilities come from its next-generation architecture and training that now covers all of life's molecules. At the core of the model is an improved version of our Evoformer module — a deep learning architecture that underpinned AlphaFold 2's incredible performance. After processing the inputs, AlphaFold 3 assembles its predictions using a diffusion network, akin to those found in AI image generators. The diffusion process starts with a cloud of atoms, and over many steps converges on its final, most accurate molecular structure.

AlphaFold 3's predictions of molecular interactions surpass the accuracy of all existing systems. As a single model that computes entire molecular complexes in a holistic way, it's uniquely able to unify scientific insights.



7BBV - Enzyme: AlphaFold 3's prediction for a molecular complex featuring an enzyme protein (blue), an ion (yellow sphere) and simple sugars (yellow), along with the true structure (gray). This enzyme is found in a soil-borne fungus (Verticillium dahliae) that damages a wide range of plants. Insights into how this enzyme interacts with plant cells could help researchers develop healthier, more resilient crops.

Source: https://blog.google/technology/ai/google-deepmind-isomorphic-alphafold-3-ai-model/

Derek Lowe on AlphaFold: Structure is Not Everything

Derek Lowe, *Science*, May 10, 2024

Derek Lowe

Now that I'm back (from some traveling) it looks like the first item of business is the advent of AlphaFold 3. That Nature preprint (which is open access) says that this extends the predictive powers of the software to other classes of molecules and to complexes between them. I had expressed some skepticism in the past about how easy that would be to do in the case of small synthetic molecules - y'know, drug candidates - and I am very interested to see how well these difficulties have been overcome.

And I think that the reason these sorts of programs seem to be more reliable than the large language models is that the grammar and vocabulary of biomolecular structure is still much more limited than that of any natural human language. It's a little more like the umpteen dozen attempts at artificial languages (Esperanto being the most famous) that have no silent letters, no irregular verbs, and generally (as compared to natural language) no layers of connotation with alternate vocabulary choices and shades of meaning. An LLM trained on Esperanto or Volapük or Loglan or whatever might well have a lower chance of confidently, fluently explaining to you that Easter this year is in July. And the hope is that diffusion-based models trained on real-world data (with some useful models thrown in, as above) will have a good chance of giving you a reasonable structure.

And I have to add the general warnings that I've been adding to this area for years. **Structure is not everything. It's very useful, very good to have, and it will accelerate a lot of really useful research. But it does not take you directly to a drug, nor to a better idea about a target for a drug, nor to a better chance of passing toxicity tests, nor to a better chance of surviving oral dosing and the bloodstream and the liver.** Better structure predictions are tools that we can use to attack those crucial problems, but they don't answer any of them. Drug discovery has not been solved by software, no matter what you might read.

Source: https://www.science.org/content/blog-post/alphafold-3-debuts

Eric Dai of Dimension Capital Puts AlphaFold 3 in Perspective

With all the (well justified) excitement around AF3, it's good to take a step back and assess where we are (and aren't). Here's my attempt at a sober, mid-development assessment.

Making first contact into multimeric co-folding of proteins with nucleic acids, proteins, and ligands/chemical matter is a foundational development. Proteins derive their function from their dynamical, highly networked interactions with the world around them. If AF2 enabled prediction of static structures of isolated proteins, then AF3 adds the additional dimension of predicting folding of interacting molecules — a key step towards improving the fidelity and relevance of these models towards drug discovery.

We can predict certain instantiations of static structure, but protein dynamics remain elusive. **We've begun to model the static structure of monomeric and multimeric proteins. However, proteins are remarkably and necessarily dynamic entities, and their function (and druggability) can rarely be modeled via static structures. Just as a viewer of a film would have an impossible time deriving its full script, score, cast and plot from a single still, so too is our ability to infer functional characteristics and druggable pockets of a protein highly limited from its AF3 representation alone.**

ML models are auto-regressive approximators of their training data — and in turn, our lack of molecular data is the key bottleneck in molecular models. We have (to my knowledge) no evidence that ML models can generate out of distribution inferences on molecular structure or function. Our ability to generate more experimental data around protein folding, molecular dynamics and molecular interactions will be the primary means by which we extend the capability set of ML for bio.

DIMENSION

Eric Dai
Investor
Dimension Capital

Protein function is only validated through experimental data. Determining (and leveraging knowledge of) structure function relationships is the central tenant of drug discovery, but this can ultimately only be accomplished through hard earned experimental and clinical validation.

We're in the early days of generating pixelated snapshots in ML x Bio. We're hitting an accelerating pace of clearing historic milestones, but the hardest work and best outcomes are yet to come.

Onwards!

Source: https://twitter.com/EricDai_BioE

Generating (Somewhat) New Biology with AI

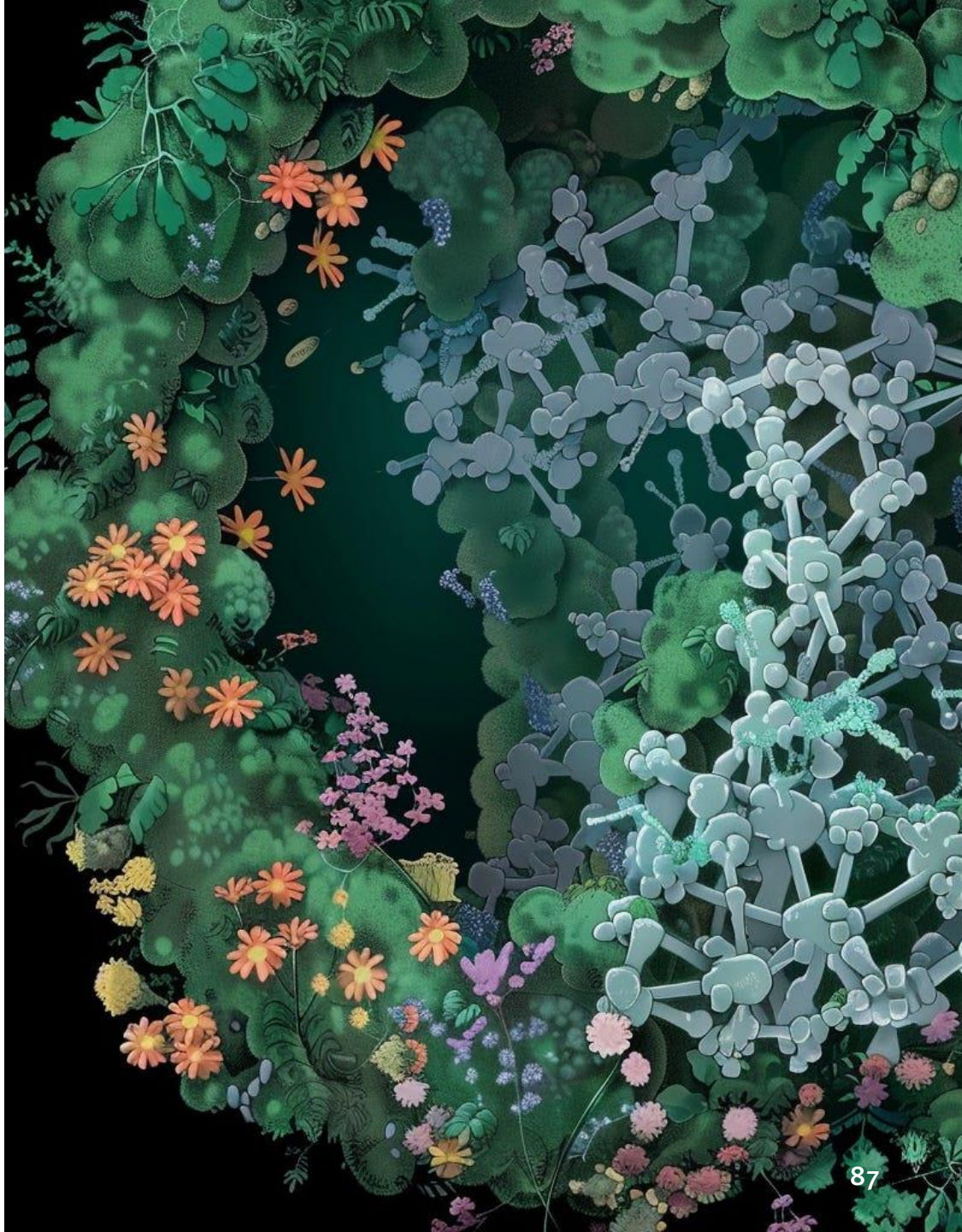
Elliot Hershberg, *The Century of Biology*, May 5, 2024

After roughly four billion years of stumbling search, Evolution has churned out an absurd diversity of organisms. Microorganisms that can convert light into energy, trees that grow to hundreds of feet in height, insects capable of farming other insects, and mammals capable of forming technological civilizations. All of this diversity is encoded in genetic information, which primarily produces a universe of molecular machines—proteins.

If the scale of organismal diversity is absurd, the universe of proteins is practically incomprehensible. The millions of unique species on Earth collectively produce somewhere around a trillion different distinct proteins. In this enormous set, there are some very pragmatic proteins responsible for building and maintaining cells and replicating DNA, but there are also more exotic machines, like the bi-directional nano-scale motors that bacteria use to navigate towards chemicals.

(continued)

Source: https://centuryofbio.com/p/digital-evolution



Hershberg on Proteins (cont)

One of the most promising fields of biotech is de novo protein design, which aims to explore the full space of possible proteins for new types of molecular machines beyond what Evolution has already produced.

This is a really big idea. Directed evolution—the set of laboratory techniques for rapidly sampling new beneficial mutations to known proteins—was a Nobel-worthy idea that has already produced a lot of value. Sampling beyond known proteins opens up an entirely new world of possibilities.

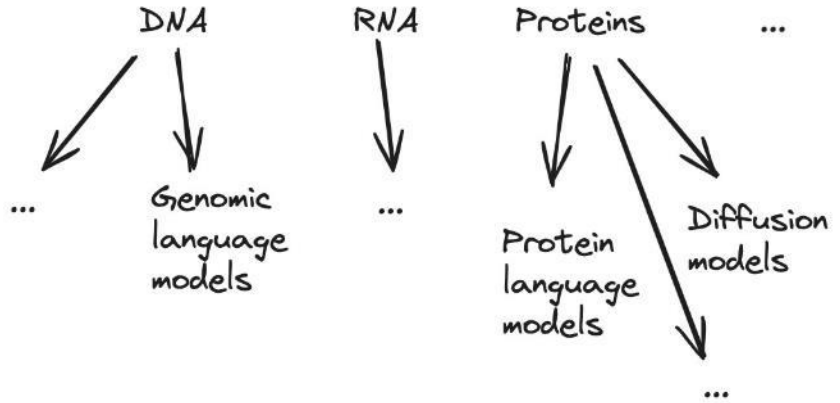
Recently, de novo protein design has gotten a big boost from AI. Taking inspiration from the wave of exciting results in using AI to generate new text, images, audio, and video, scientists have retrofitted and repurposed the underlying algorithms to generate new proteins.

This isn't just a big idea—it's apparently a billion dollar idea. Last week, a new startup called Xaira Therapeutics announced its $1B Seed round of financing. David Baker, the senior author of the paper with the figure above, is a co-founder. While the vision for the company spans everything from basic biological research to clinical trial design, a major focus is to design new antibody therapies by improving recent generative AI algorithms from the Baker Lab.

So, when people say "generative AI for biology," they are talking about the development of deep learning models capable of generating new types of biological outputs—like new DNA sequences or proteins. In the future there may be models trained on a variety of inputs capable of producing a variety of outputs, but right now, most efforts are focused on using specific algorithms for specific biological inputs/outputs.

These models and their outputs have been getting a lot of attention. Last week, a bioRxiv preprint from Profluent Bio describing new AI-generated CRISPR proteins took the Internet by storm. And it wasn't just my corner of the Internet with other biotech nerds—The New York Times covered the work the same day it was posted.

Source: https://centuryofbio.com/p/digital-evolution



According to the NYT article, Profluent's model "analyzes the behavior of CRISPR gene editors pulled from nature and learns how to generate entirely new gene editors." I think this is close to true, but not quite right.

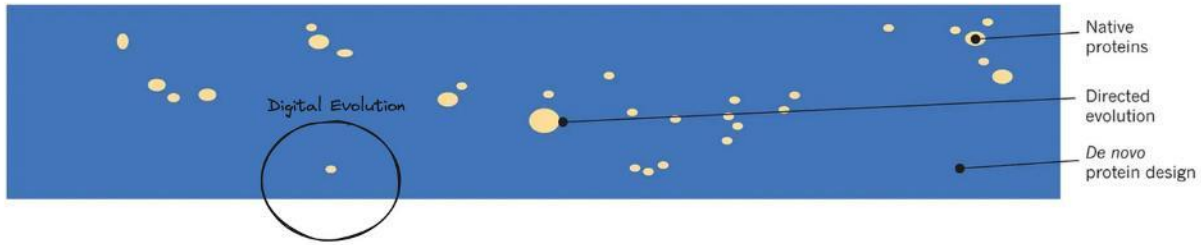
In a clever piece of detective work, Brian Naughton, a biological data science guru, asked a simple question: how distant are these new gene editors from multiple natural sequences? When lining up the new editors against naturally occurring proteins, he realized that he could "recreate 98% of the sequence (all but 24 amino acids) with 3 Streptococcus sequences."

A section of Brian's CRISPR sequence alignment.

I don't think Brian intended for this to be a dunk on Profluent's work, and I don't either. It would be effectively impossible for even the best CRISPR biologist to sit down at their keyboard and type out this new sequence, let alone confidently predict that it would actually work in cells. Clearly, in its exhaustive training on natural sequences, Profluent's model is learning something really interesting about how CRISPR proteins work. But the generated results aren't entirely new. They are like one of Dali's surrealist paintings, synthesizing disparate existing objects into a new unified whole. The novelty is in the composition, not the ingredients—which come from Nature. (continued)

Hershberg on Proteins (cont)

One way to look at this is that it's like Digital Evolution, where the AI algorithm is sampling from the space of all possible CRISPR permutations.



This makes a lot of sense when considering how these models work. To understand all of this, we're going to look under the hood of this specific approach. This will help bootstrap intuition for what we should expect—and not expect—from this first wave of generative AI models for biology.

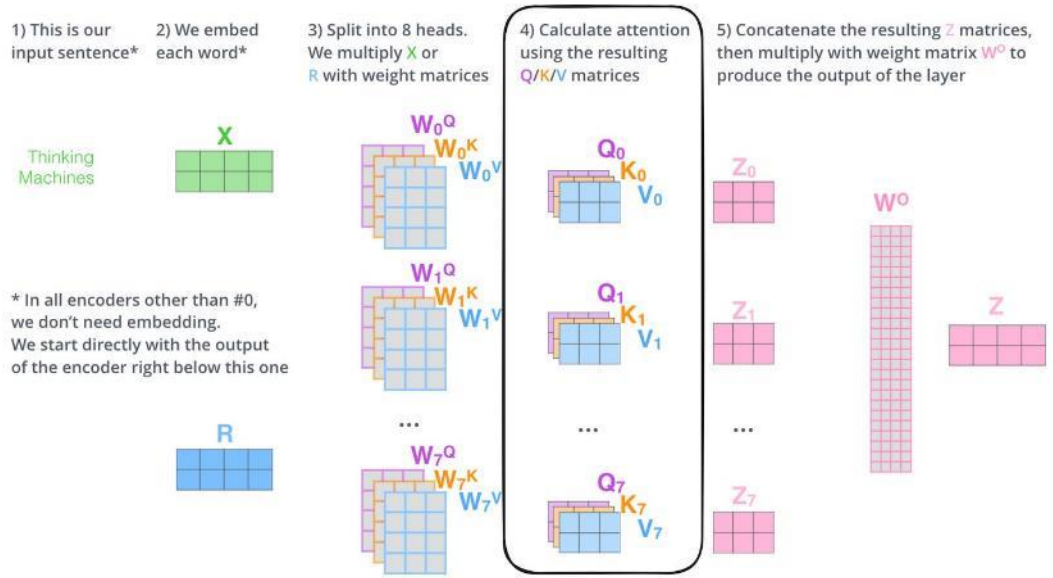
A Quick Primer on Attention

When analyzing the growth of scientific knowledge, there are often fundamental results that seed important branching points in our understanding or capabilities. For the current wave of AI progress, that critical node is a 2017 paper from Google entitled Attention is All You Need.

This paper described a new neural network architecture called a Transformer. At its core, a neural network is a big pile of linear algebra that learns the relationship (function) between inputs and outputs. These learned functions can be used to solve hard problems like language translation that are difficult—or impossible—to produce solutions for by explicitly writing code.

In theory, given enough time and training examples, even the simplest neural networks can learn to approximate nearly any function. But we don't live in the world of theory, so AI researchers need to invent new architectures, which are specific combinations of the underlying linear algebra operations that converge on interesting solutions in a reasonable amount of time.

So in reality, one of the layers in a Transformer model look something like this:

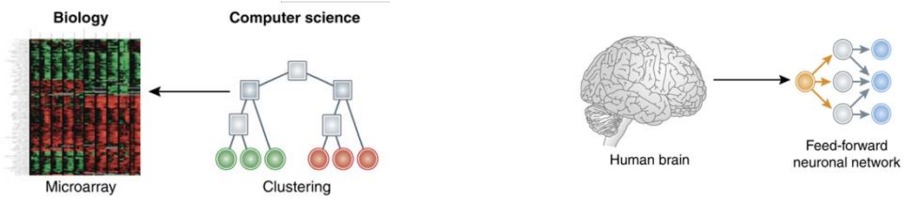


... For now, here are the three takeaways we need to understand:

1. Neural networks learn to approximate complex functions, like language generation, by repeatedly tuning weights to perform better on training examples.
2. An important neural network architecture is the Transformer. These models have specific sets of matrices that track relationships between the elements of their input. This is called attention.
3. One of the best ways to train Transformers is to mask parts of the input and make the model correctly guess what is being hidden.
4. With these basics in mind, we're in a better place to understand how these protein language models are generating new CRISPR sequences. (continued)

Hershberg on Proteins (cont)

Biology and computer science have a unique bidirectional relationship. Studying biological computation gives us new ideas for how to program computers. The connections between biological neurons provided inspiration for artificial neural networks. Algorithms from computer science are also useful tools for learning new things about biology.



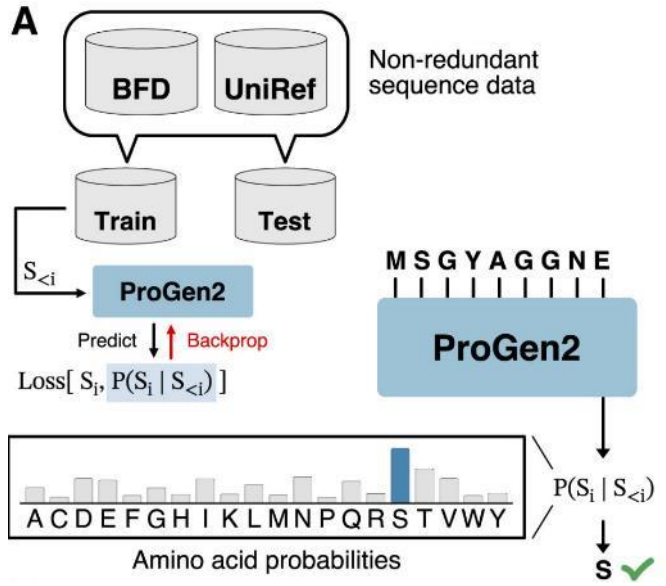
As the mountain of new machine learning techniques grows exponentially, cleverly repurposing these tools for biological purposes has become its own kind of art form. Around the time that language models started to really work, computational biologists started to have more success modeling proteins using these types of approaches.

Interestingly, many of the earliest results can be traced directly to new biotech startups. Surge Biswas, one of the lead authors of a 2019 protein modeling paper from the Church Lab, is now the co-founder and CEO of Nabla Bio. Alex Rives, one of the leader authors of a 2019 protein language model paper, is now the interim CEO of EvolutionaryScale. And Ali Madani, lead author of a 2020 paper on protein language models, is the CEO of Profluent, the company that announced the AI-designed CRISPR proteins last week.

In the 2020 paper and a pair of follow-up papers in Cell Systems and Nature Biotech in 2023, Madani and his colleagues developed and scaled causal language models for the task of generating new protein sequences.

Let's think back to how this strategy works in the context of natural language. The causal training setup involves masking the last word in a string of words, and making the model guess what is based on the attention patterns in the rest of the string. Once the model is trained, this prediction step can be repeated to complete an entire sentence.

Instead of predicting the next word in a sentence, the model—called ProGen2—is predicting the next amino acid building block in a protein.



And just like a language model can be used to generate new sentences, ProGen2 can be used to generate new proteins.

This is how Profluent generated new CRISPR proteins last week. There's only one more core detail we need to understand about their process: fine-tuning. The masking trick we've talked about is typically used as a pre-training step in developing Transformer-based Large Language Models (LLMs) for language applications. This step learns a general representation of language, before training a model on a more specific downstream task.

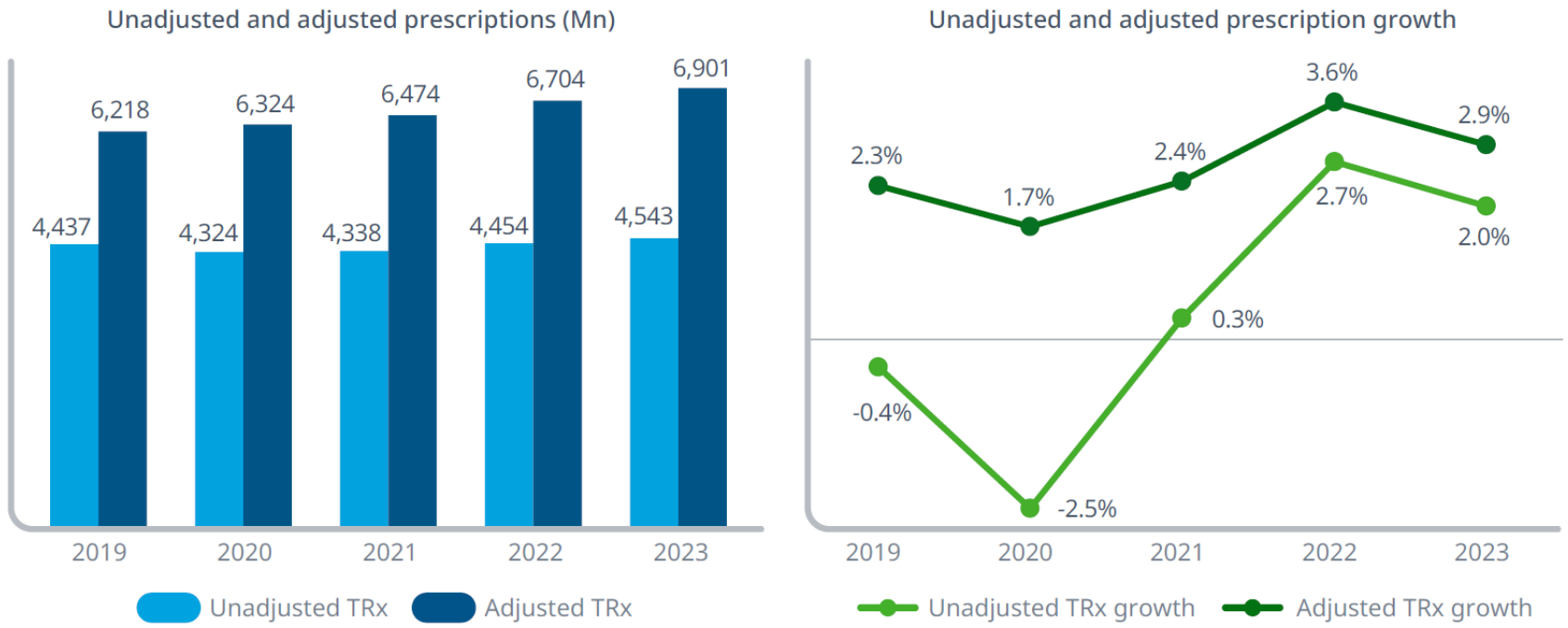
As the entomologist E.O Wilson once framed it, "The real problem of humanity is the following: we have Paleolithic emotions, medieval institutions, and god-like technology." As we come to learn the language of Evolution and refine our capacity to steer it, we need to solve the complex human challenges that are rate-limiting broader access to better health. (continued)

IQVIA Institute Report on U.S. Use of Medicines

IQVIA Institute Report (May 7, 2024): Use of Medicines in the U.S. Rising Slowly Over Time

Dispensed prescriptions reached 6.9Bn in 2023, with 2.9% growth compared to 2022

Exhibit 8: Unadjusted and adjusted dispensed prescriptions (Mn) and growth, 2019–2023

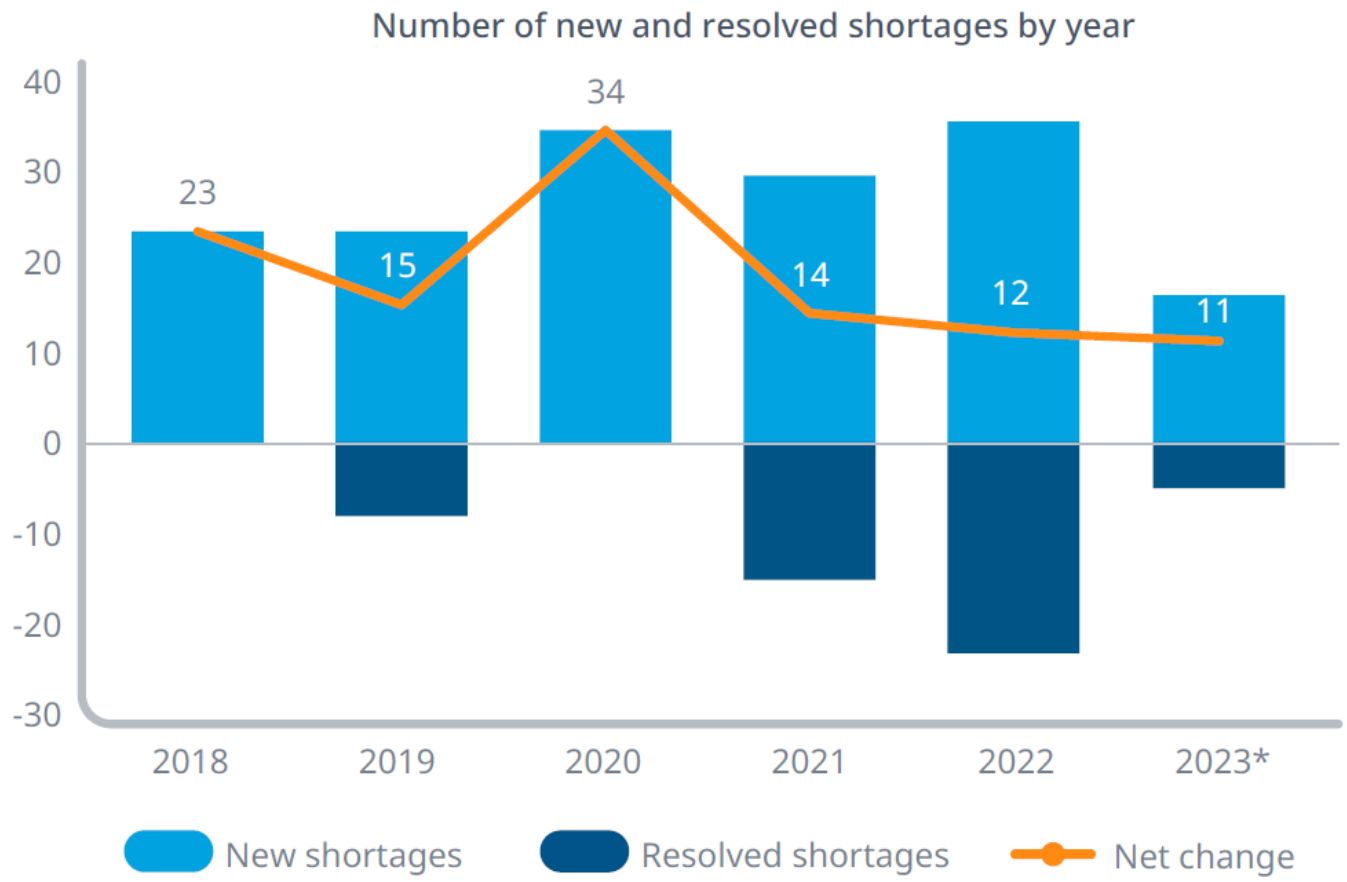


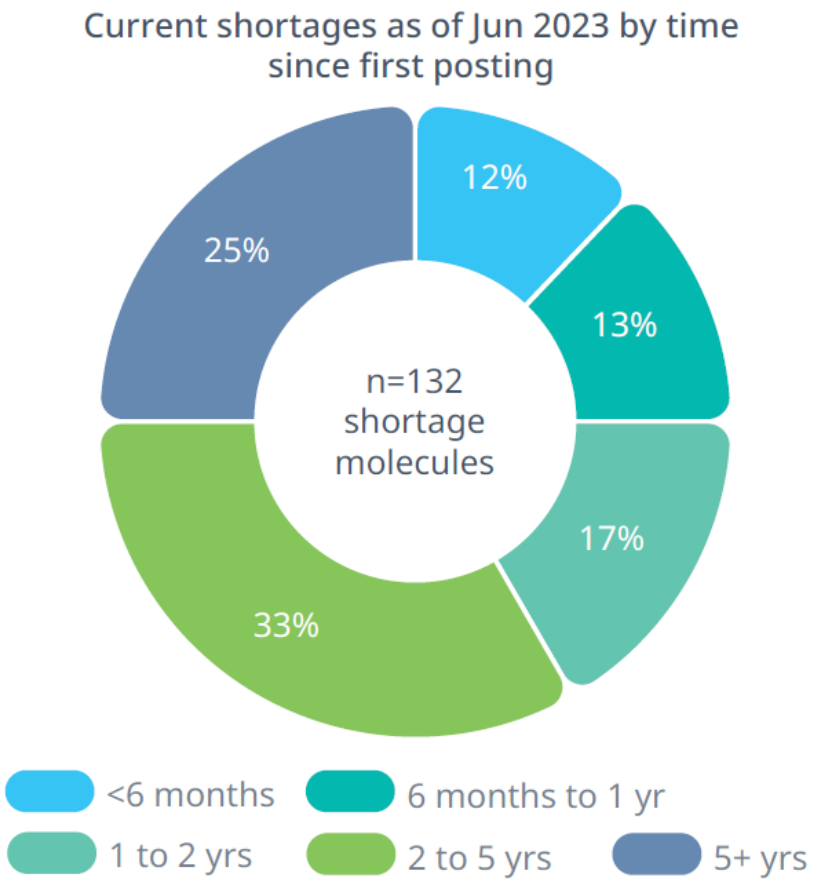
Source: IQVIA National Prescription Audit, Dec 2023; IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

More shortages continue to be reported than resolved with 58% of current shortages ongoing for more than two years

Exhibit 11: Net shortage increase by year and time since first posting of current shortages





Source: Drug Shortages in the U.S. 2023: A Closer Look at Volume and Price Dynamics, Nov 2023. Report by the IQVIA Institute for Human Data Science.
*2023 is through June

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

Immunology / Obesity Drug Utilization Growing While Use of Routine Contraception is Declining

Notable shifts and impacts in medicine use occurred across therapy areas in the U.S. in recent years

Exhibit 12: Notable trends in medicine use in 2023

Growing use of immunology treatments

- **Immunology** drug use reached **1.2Bn days of therapy** in 2023, **up 60%** from 2019.
- Treatment of **Crohn's disease and psoriasis** accounted for **26% and 15% of growth**, respectively.

Drug shortages impacting patient care

- Since 2018, an average **25 new molecule shortages** have occurred annually.
- As of June 2023, there were **132 active shortages** with **58%** on shortage for **over 2 years**.

Rising use of novel obesity drugs

- **Nearly 700K GLP-1 agonist** new prescriptions across diabetes and obesity in February 2024, **up 181%** compared to two years prior.

Combatting the opioid overdose epidemic

- Per capita prescription **opioid use down 67%** since the peak in 2011.
- **Over-the-counter naloxone** available in 2023 **accounts for 15%** of volume in Jan-Feb 2024.

Antibiotic use and rising antimicrobial resistance

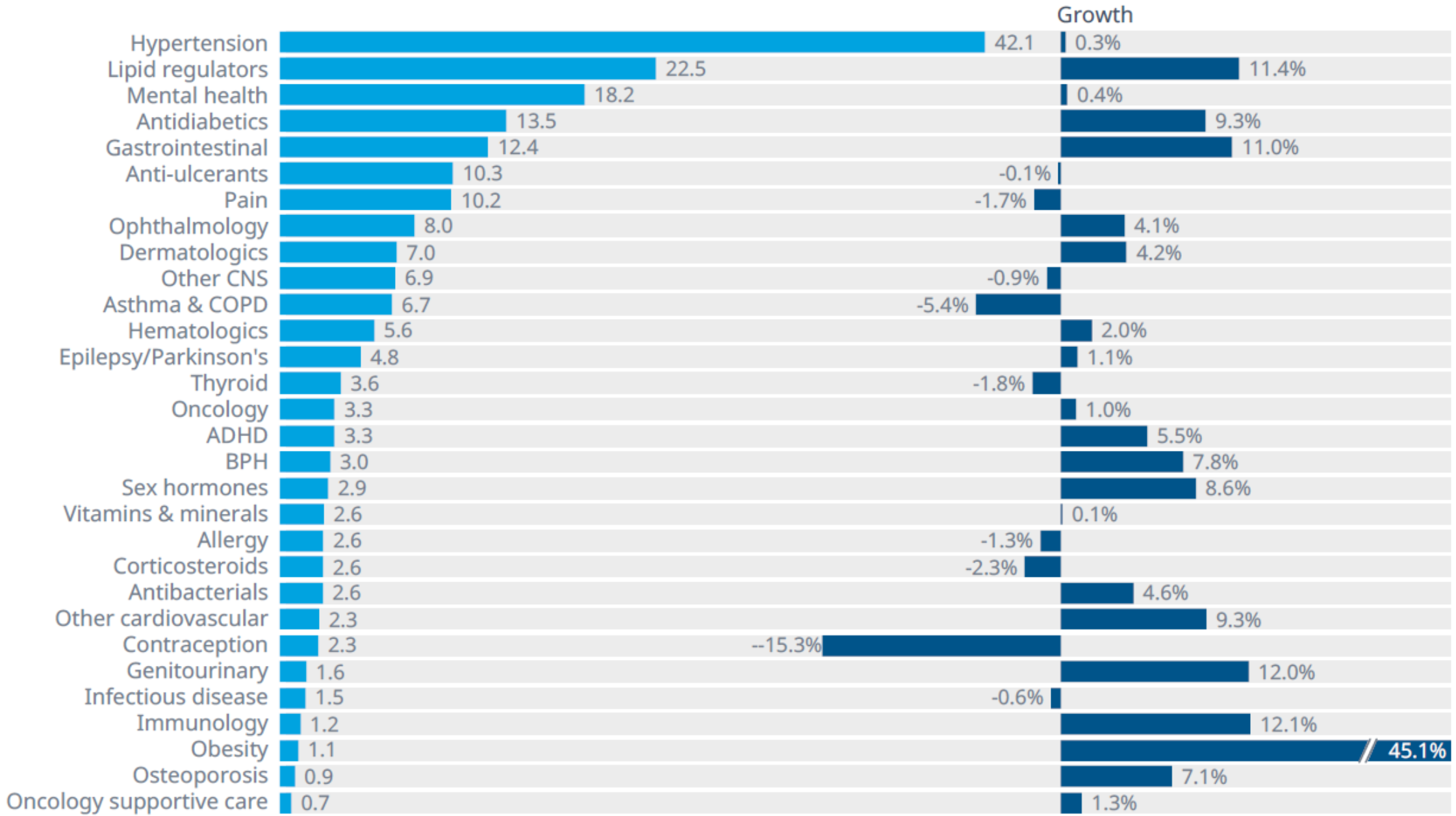
- **2.6Bn antibiotic days of therapy** in 2023, returning to pre-pandemic levels.
- use in **children and older adults up 4–12%** in Q4 2022 from historic seasonal levels.

Changing patterns of contraceptive use

- **Routine contraception use down 3%** in 2023 with **25Mn fewer** days of therapy.
- **Emergency contraception** use and **sterilization visits up 35% and 11%** from 2021, respectively.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

Exhibit 13: Top 30 therapy areas by defined daily doses (DDDs) 2023 (Bn) and % growth from 2022

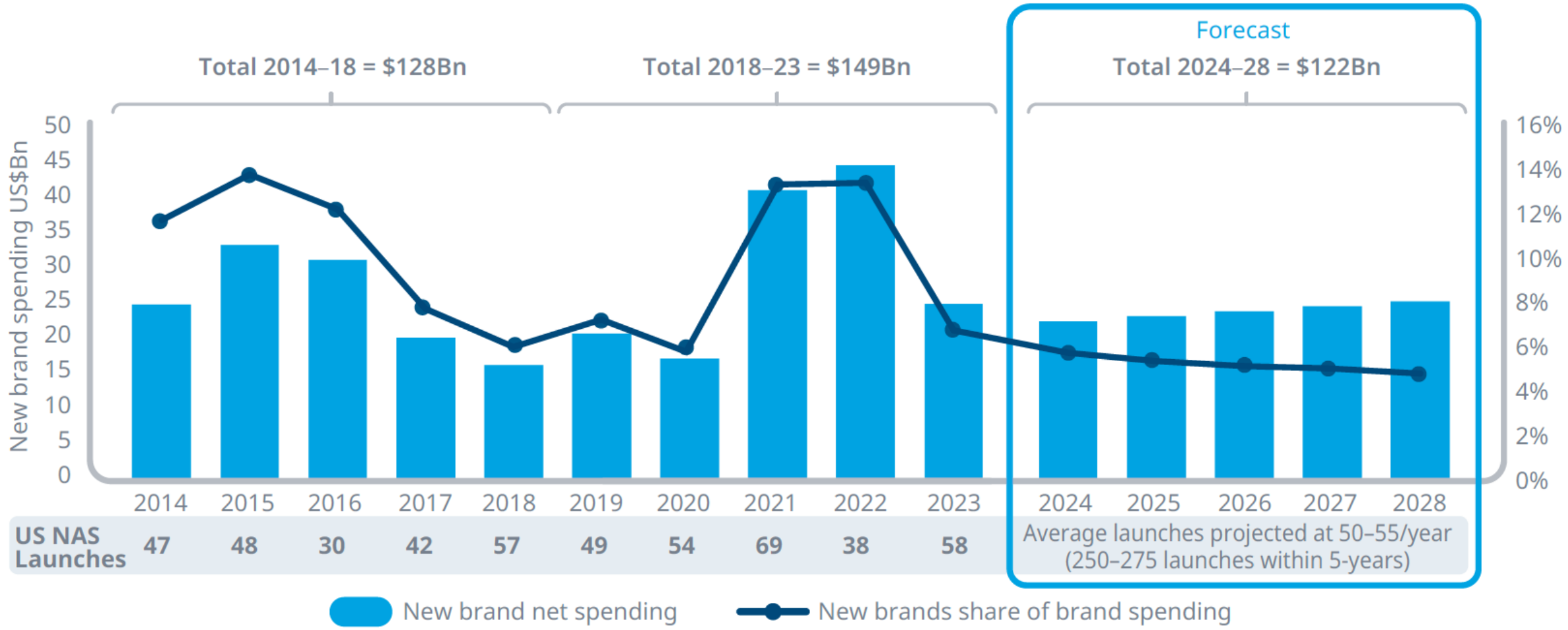


Source: IQVIA National Sales Perspective, Dec 2023; IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

New brand spending in the U.S. is projected to be higher than the last 5 years but a smaller share of spending

Exhibit 51: U.S. new brand spending

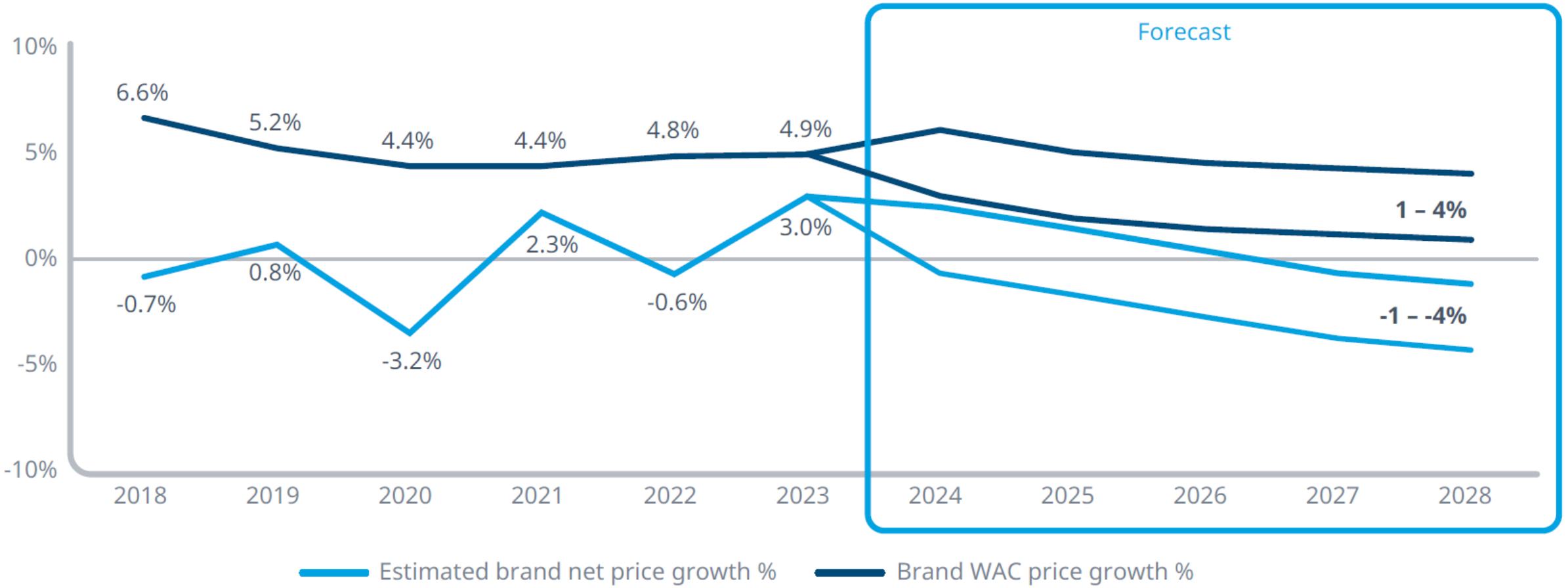


Source: IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

Net prices for protected brands are forecast to decline -1 to -4%, while list prices will grow 1 to 4% including impact of price cuts

Exhibit 52: Wholesaler Acquisition Cost (WAC) growth and net price growth for protected brands

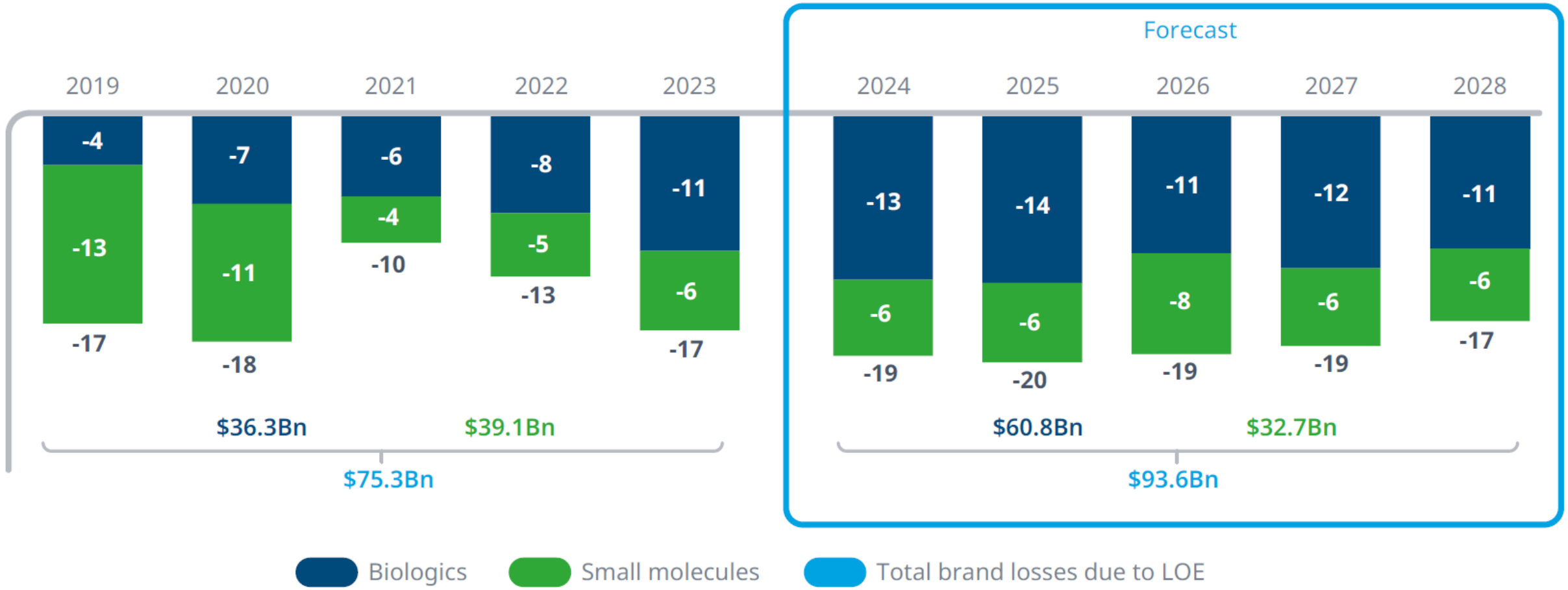


Source: IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

The impact of exclusivity losses will increase to $93.6Bn over 5 years including significant biosimilars

Exhibit 53: U.S. impact of brand losses of exclusivity 2019–2028, US$Bn

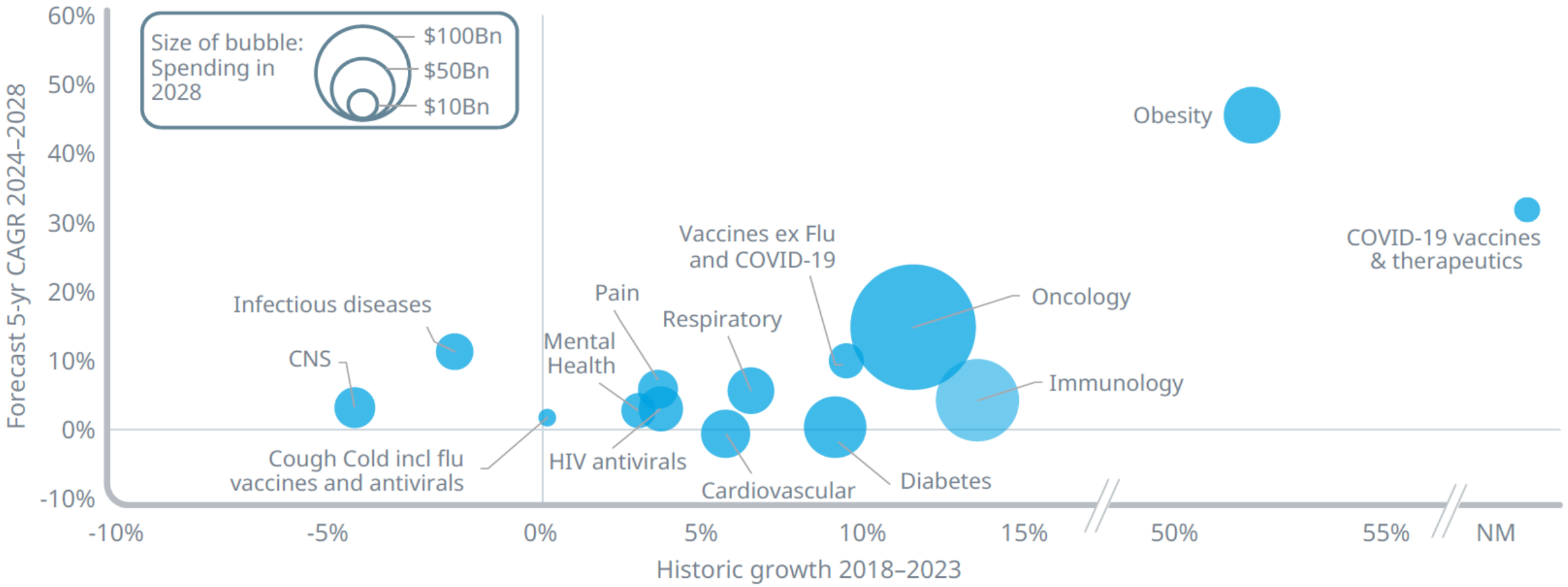


Source: IQVIA Market Prognosis, Mar 2024; IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

Oncology and obesity drive growth through 2028 while diabetes, immunology and COVID-19 contribute to slowing

Exhibit 54: Historic and forecast net spending growth for leading therapy areas

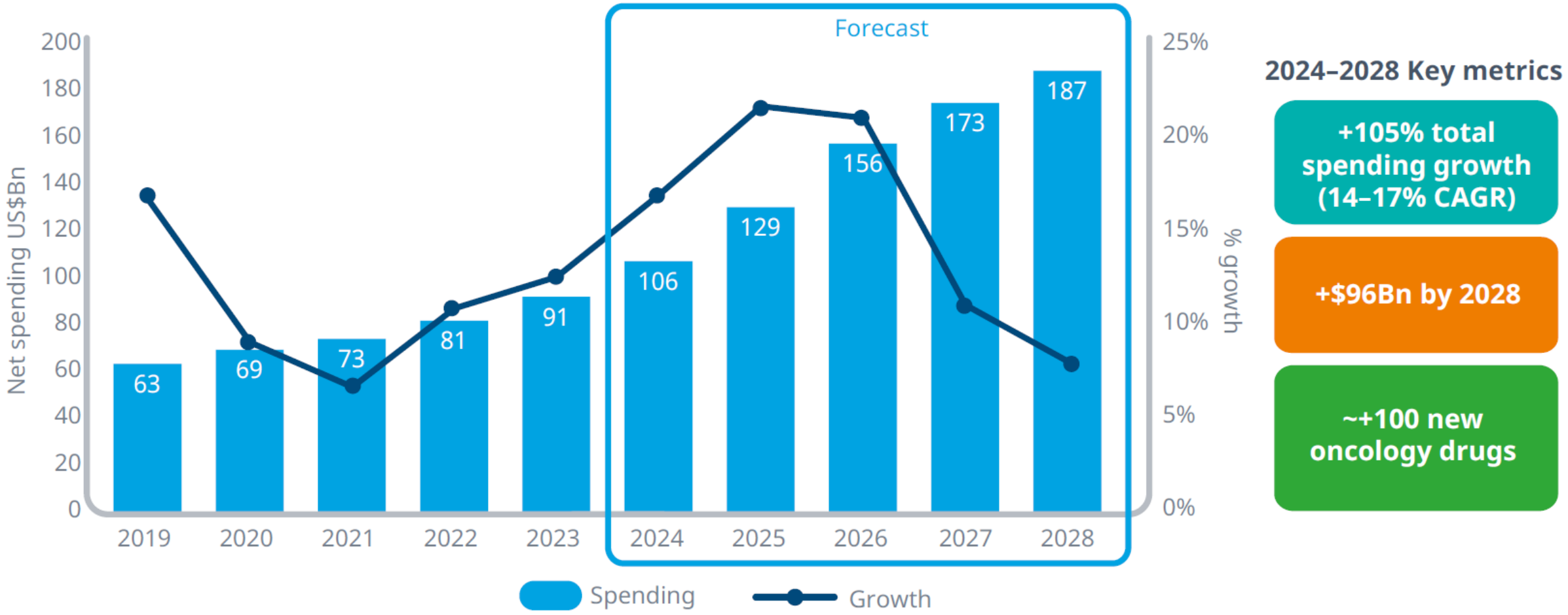


Source: IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

U.S. oncology spending to reach $187Bn by 2028, with growth slowing to 8% from biosimilar savings late in the forecast

Exhibit 55: Oncology spending at estimated manufacturer net prices, US$Bn

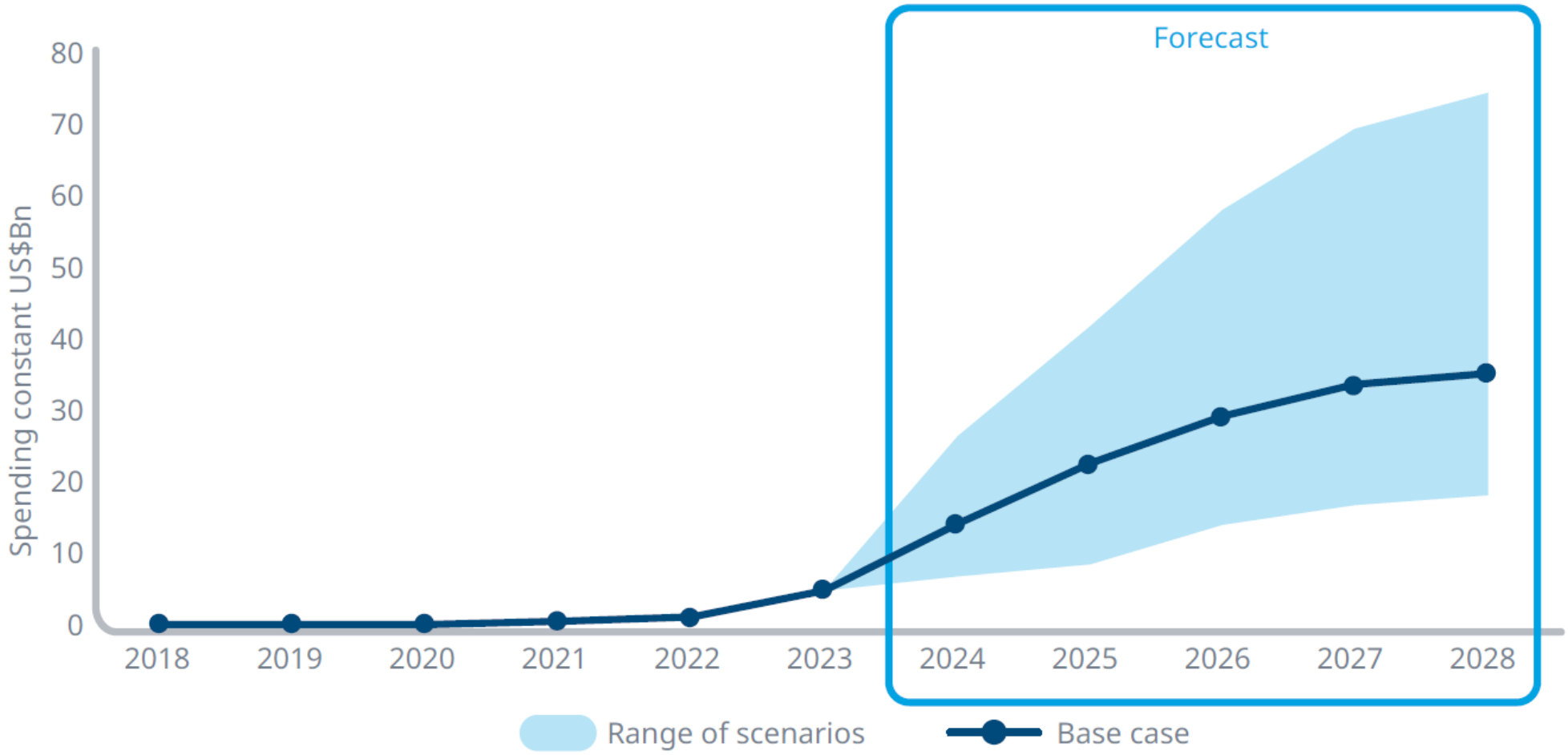


Source: IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

Spending on obesity drugs has accelerated in the past 2 years from novel GLP-1 inhibitors with upside if more widely reimbursed

Exhibit 59: Obesity spending at estimated manufacturer net prices, US$Bn



2024–2028 Key metrics

High scenario $200Bn+ invoice spending / net $73Bn based on significant expansion in usage and reimbursement

Base case $96Bn invoice spending / net $35Bn as a mix of patient payment, industry assistance, new care delivery paradigms augment limited traditional payer reimbursement

Low scenario $50bn invoice spending / net $18Bn in low scenario where access remains limited and costly to patients

Source: IQVIA Institute, Mar 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2024

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