Biopharmaceutical Sector

Weekly Update – November 20, 2023

STIFEL | Healthcare

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Recent issues in case you missed and want to read:

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)
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September 5, 2023 (FTC, IRA, Depression)
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August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
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July 1, 2023 (Obesity drugs)
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June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Join Us at These Upcoming Events

Biotech Hangout held its latest event on November 17.

The next event will be on December 1, 2023.

Please join us.

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

The week of Jan 7, 2024 will feature over 30,000 biopharma professionals in SF for JPM, Biotech Showcase and many other events. Stifel will be hosting an industry cocktail party on Jan 7th.

To meet with Stifel
yeungn@stifel.com

Macro Update

Positive US Inflation Number on Nov 14, 2023

Consumer prices rose 3.2 percent in the year through October, decelerating from the previous month and showing encouraging signs under the surface.

Source: https://www.nytimes.com/live/2023/11/14/business/cpi-inflation-fed

The Case for Two Fed Rate Cuts in Early 2024 Is Building

Conor Sen, *Bloomberg* (opinion), Nov 17, 2023 (excerpt)

Now that there's a growing consensus that the Federal Reserve is done raising interest rates — a shift I predicted last month — it's time to ponder when policymakers will consider cutting rates and by how much.

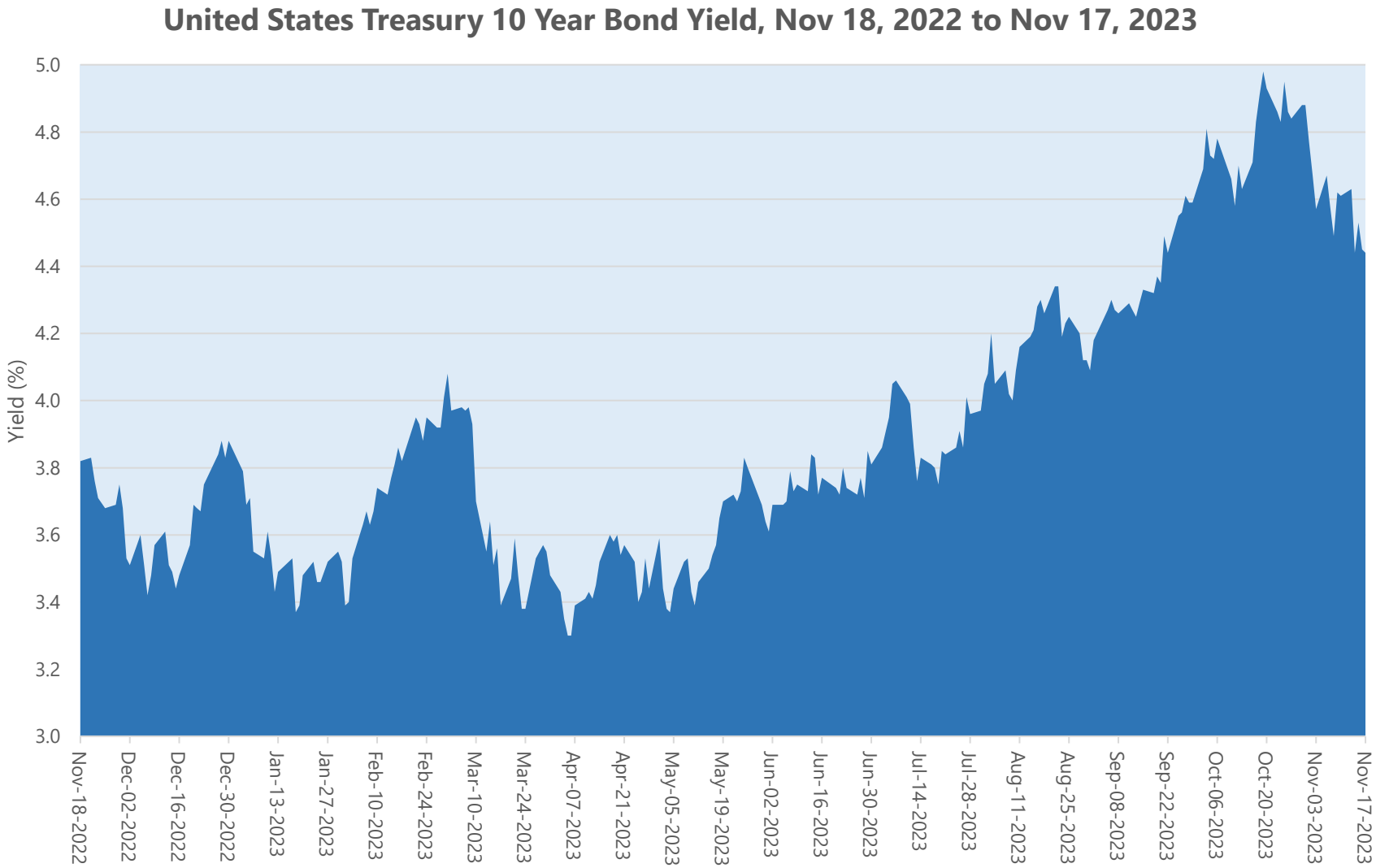
It's common to think that wouldn't happen until inflation returns to the Fed's 2% target or the risk of recession is elevated. The first rate cut should and will happen sooner than that and not because of a dramatic slowdown in the economy. Given how the labor market and inflation have evolved, cutting rates by 50 basis points in the first half of 2024 would serve to preserve the expansion while maintaining a policy stance that's at least somewhat restrictive and continuing to put downward pressure on prices.

Fed policymakers are unlikely to discuss the possibility of a rate cut at least until their December meeting. But since their last set of economic projections in September, both the labor market and inflation have trended weaker than their estimates — one obvious reason for them to shift from a rate-hike to a rate-cut bias.

Importantly, at a time when policy is restrictive, the Fed can't afford to wait until inflation is all the way back at 2% or the labor market is showing signs of dramatic weakness — by then the economy would likely already be in recession, which the central bank wants to avoid. Policymakers will want to be somewhat proactive. That's where the idea of surgical rate cuts comes in — a possibility I raised last week, piggybacking on Powell's "significantly restrictive" language.

Source: https://www.bloomberg.com/opinion/articles/2023-11-17/the-case-for-two-fed-rate-cuts-in-early-2024-is-building

Big Climb in Long Treasury Yields Has Reversed



Ten-Year US Treasury Bond Yields have dropped by over 50 basis points since peaking a month ago.

That's a huge move and a big positive for biotech.

Source: S&P CapitalIQ.

Japan’s Economy Contracts as Recession Risks Grow

Tetsushi Kajimoto and Leika Kihara, Reuters, Nov 15, 2023 (excerpt)

TOKYO, Nov 15 (Reuters) - Japan's economy contracted in July-September, snapping two straight quarters of expansion on soft consumption and exports, complicating the central bank's efforts to gradually phase out its massive monetary stimulus amid rising inflation.

The data suggests stubbornly high inflation is taking a toll on household spending, and adding to the pain for manufacturers from slowing global demand including in China.

"Given the absence of a growth engine, it wouldn't surprise me if the Japanese economy contracted again in the current quarter. The risk of Japan falling into recession cannot be ruled out," said Takeshi Minami, chief economist at Norinchukin Research Institute.

"The weak growth and the spectre of slowing inflation could delay the BOJ's exit from negative interest rates," he said.

Gross domestic product (GDP) in the world's third-largest economy contracted 2.1% in the third quarter, government data showed on Wednesday, a much larger decline that a median market forecast for an annualised 0.6% fall. It followed an expansion of 4.5% in the previous quarter.

Slowing inflation and growth in Japan is negative for the Yen as the need to lower rates grows. Lower rates incentivize Japanese savers to leave the currency which is bad for the exchange rate. This, in turn, will make it more difficult for Japan pharma to engage in outbound M&A deals.

Source: https://www.reuters.com/markets/asia/japans-economy-contracts-demand-wanes-2023-11-15/

Biopharma Market Update

Ono Pharma HQ, Osaka, Japan

XBI Closed at 72.66 Last Week (Up 9.1%)

The XBI headed up last week for the second time in three on the back of a very good CPI Inflation number. The XBI is up 13.3% from its low point of 64 on Oct 27th (three weeks ago).

Biotech Stocks Up Last Week

Return: Nov 11 to Nov 18, 2023

Nasdaq Biotech Index: +2.1%
Arca XBI ETF: +9.1%
Stifel Global Biotech EV (adjusted): 9.8%*
S&P 500: +2.2%

Return: Jan 1 to Nov 18, 2023

Nasdaq Biotech Index: -7.1%
Arca XBI ETF: -12.5%
Stifel Global Biotech EV (adjusted): -5.7%*
S&P 500: +17.5%

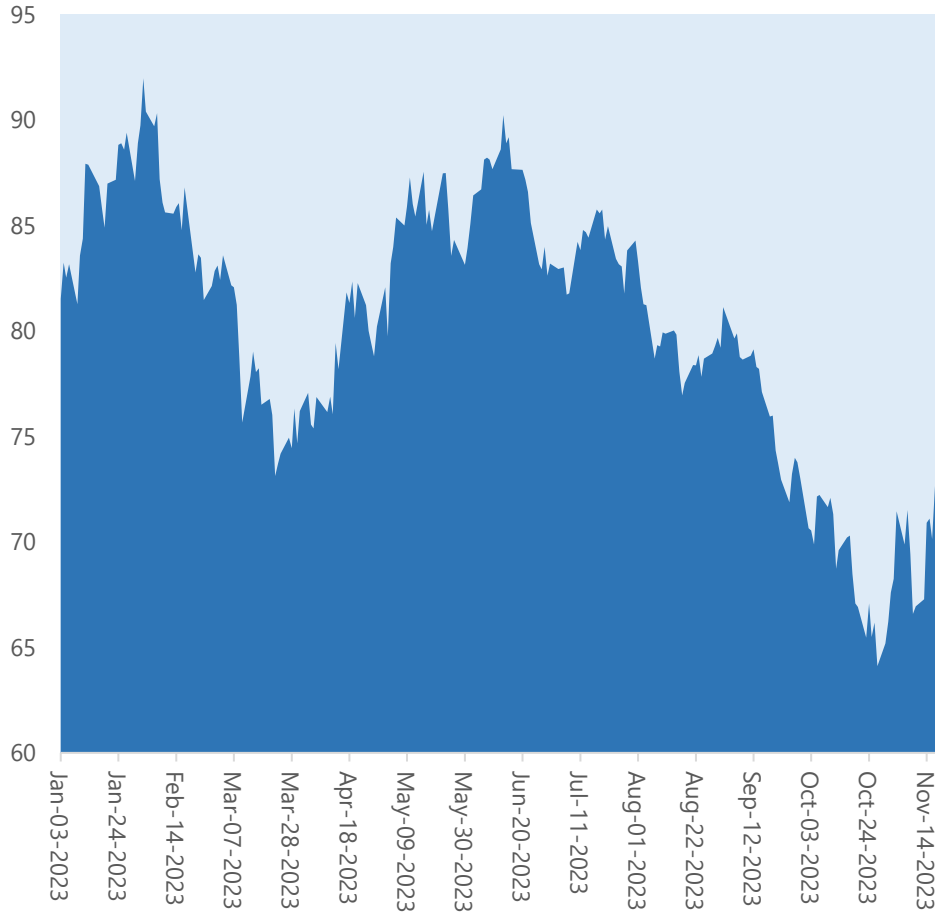
VIX Down

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Nov 10: 14.2%
Nov 17: 13.8%

10-Year Treasury Yield Down

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 27: 4.86%
Nov 10: 4.61%
Nov 17: 4.44%

XBI, Jan 3, 2023 to Nov 17, 2023

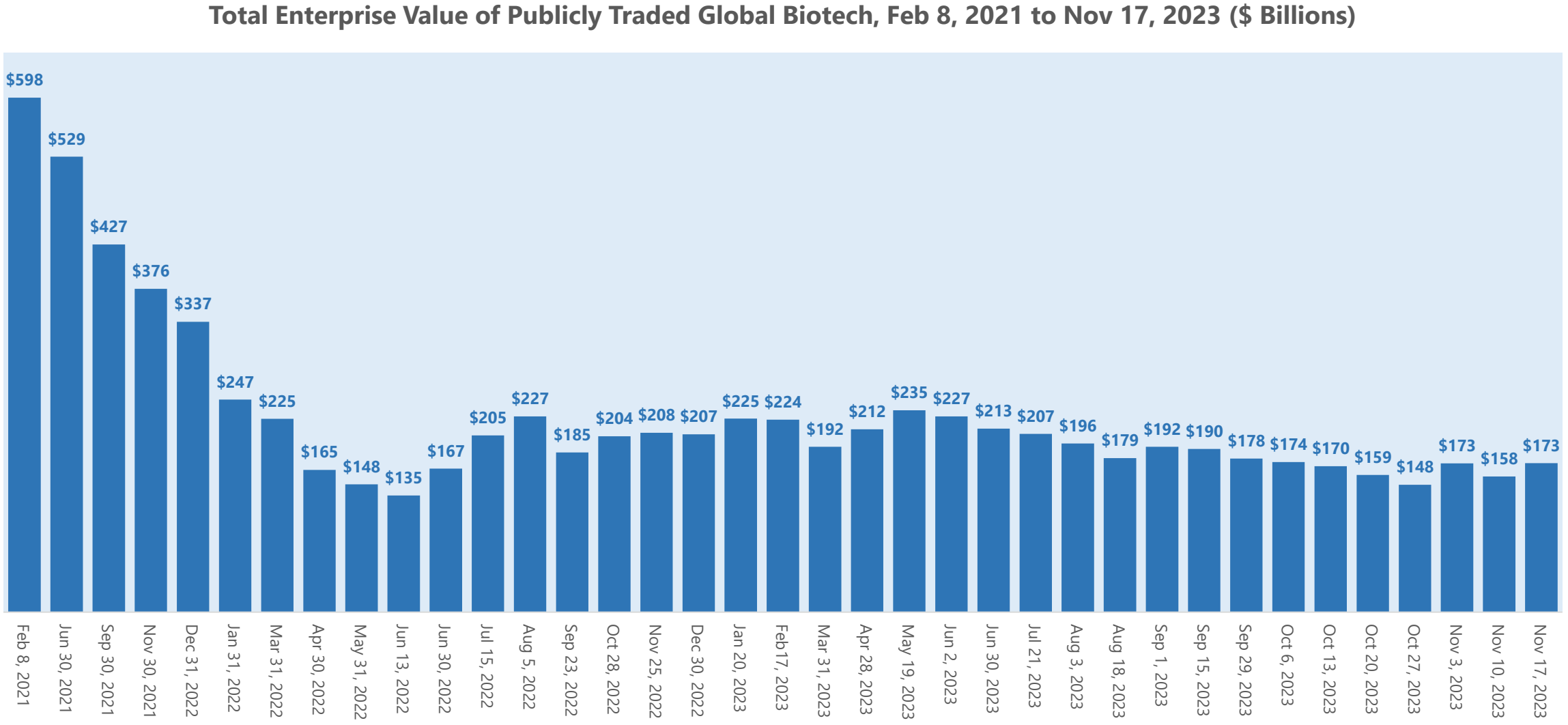


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Rose Significantly Last Week

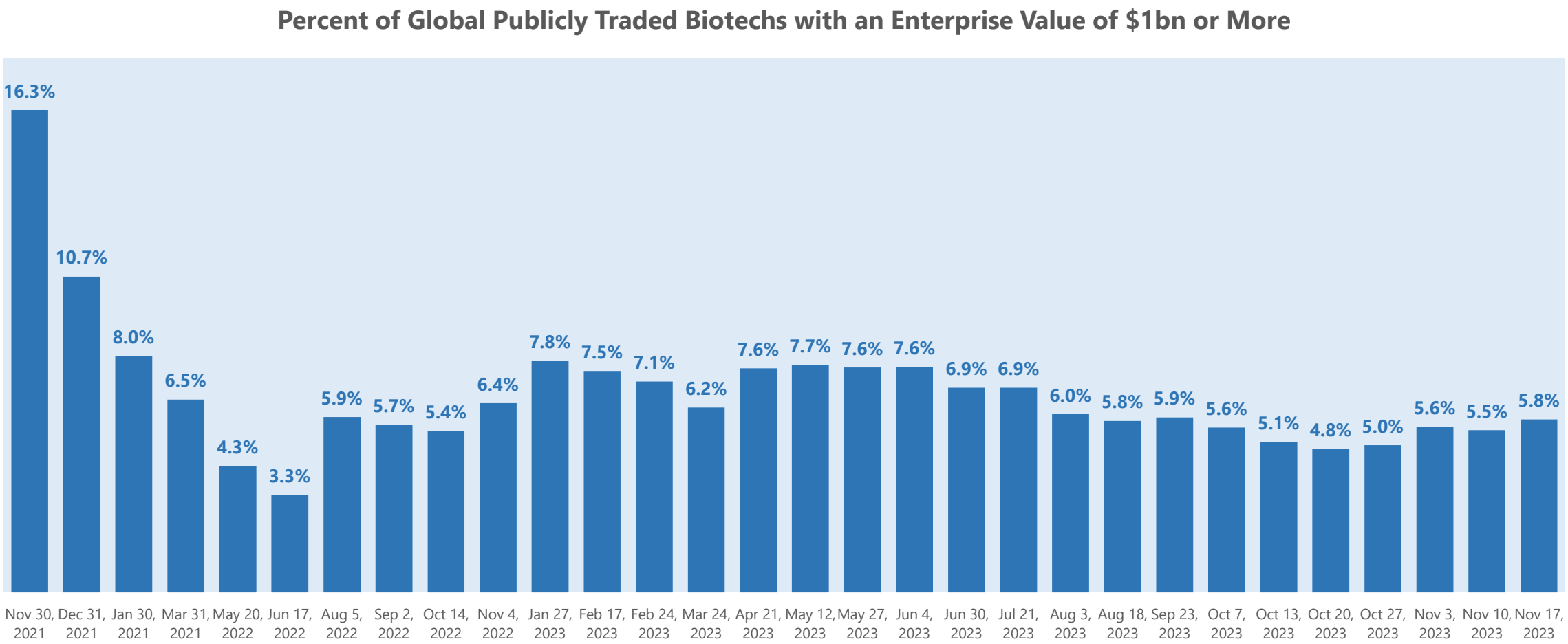
The total enterprise value of the global biotech sector rose by 9.8% last week and is now down 5.7% for the year after adjusting for exits and entries.



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

The “Rich” Neighborhood in Biotech is Getting Bigger

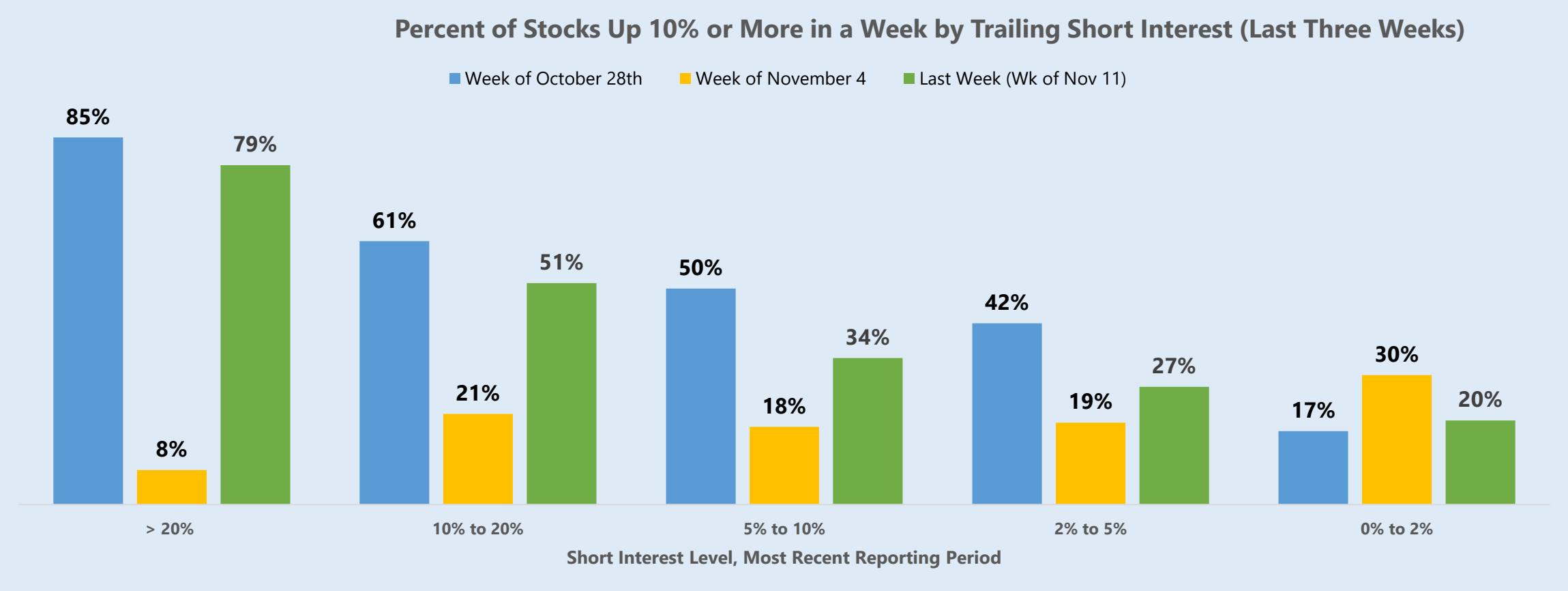
As of last Friday, 5.8% of public biotechs around the world had an enterprise value of $1bn or more. Compare this to 4.8% five weeks ago.



Source: CapitalIQ.

More Short Covering Last Week

Three weeks ago (week of October 28) witnessed a 14% bump in biotech in a week and concentration of big gains in heavily shorted stocks. The next week saw stocks drift down on little news and heavily shorted stocks performed poorly. Last week saw a 9% bump in the XBI and, also, heavy concentration of gains in stocks that were heavily shorted. It was obviously another short covering week (but not as much as in three weeks ago). We can only surmise that it has been a stressful month for funds that rely heavily on short selling.



Source: S&P CapitalIQ. Short interest is defined as number of shares short divided by total shares outstanding.

October a Tough Month for Life Science Hedge Funds

Institutional Investor, Nov 14, 2023 (excerpt)

Casdin has been badly hurt by BioLife Solutions, its largest long for most of the year. The stock is down more than 40 percent for the year and fell about 27 percent in October alone. In the third quarter, Casdin boosted its stake in the company, a supplier of cell-processing tools and services for the cell and gene therapy and broader biopharma markets, by about 13 percent.

Other funds suffered smaller, but nonetheless sizable, losses last month. For example, Perceptive Advisors dropped 9.5 percent in October and is down about 9.3 percent for the year. The hedge fund firm's largest long, Amicus Therapeutics, fell nearly 10 percent in October.

On the other hand, American depositary shares of LianBio, its third-largest long, surged 170 percent last month. In late October, the company announced an agreement with Bristol Myers Squibb for the exclusive rights to develop and commercialize mavacamten, a cardiomyopathy drug, in several Asian markets. LianBio will receive $350 million up front.

RA Capital Management's hedge fund declined by about 8.9 percent last month and is down 8.6 percent for the year. Its largest long, Ascendis Pharma, which accounted for nearly 19 percent of the firm's assets at the end of the second quarter, fell 4.6 percent in October. RA Capital had boosted this stake by more than 61 percent during the third quarter.

Armistice Capital, meanwhile, dropped 7.6 percent last month and is down 9.6 percent for the year. Soleus Capital Master Fund lost 7.7 percent last month, plunging into the red by 6 percent for the year. It was one of the few biopharma-oriented hedge funds to make money last year.

Elsewhere, Braidwell, which launched last year, declined by 8.6 percent in October and is off by 1.4 percent for the year. Avoro Capital Advisors fell 1 percent for the year, extending its loss for the year to 13.8 percent. EcoR1 Capital Management dropped just 70 basis points and is down about 13 percent for the year.

Two funds bucked this losing trend. Cormorant Global Healthcare Master Fund tacked on 50 basis points last month and is now up 21 percent for the year. Institutional Investor previously reported that Cormorant had been boosted by its largest long position, MoonLake Immunotherapeutics, which accounted for nearly one-quarter of Cormorant's U.S.-listed long assets at the end of the second quarter.

Averill Partners, known for its short-selling acumen, gained slightly last month and is now up about 15 percent for the year.

We speculated a few weeks ago that October could not have been a good month for the hedge fund community and that perhaps this explains some of the non-responsiveness of the market to positive news.

Indeed, it appears that October was a bad month for most life science hedge funds.

There have been winners, of course, such as Averill, Cormorant and Deep Track.

We are hearing that a number of funds are shifting to a net long position in recent weeks.

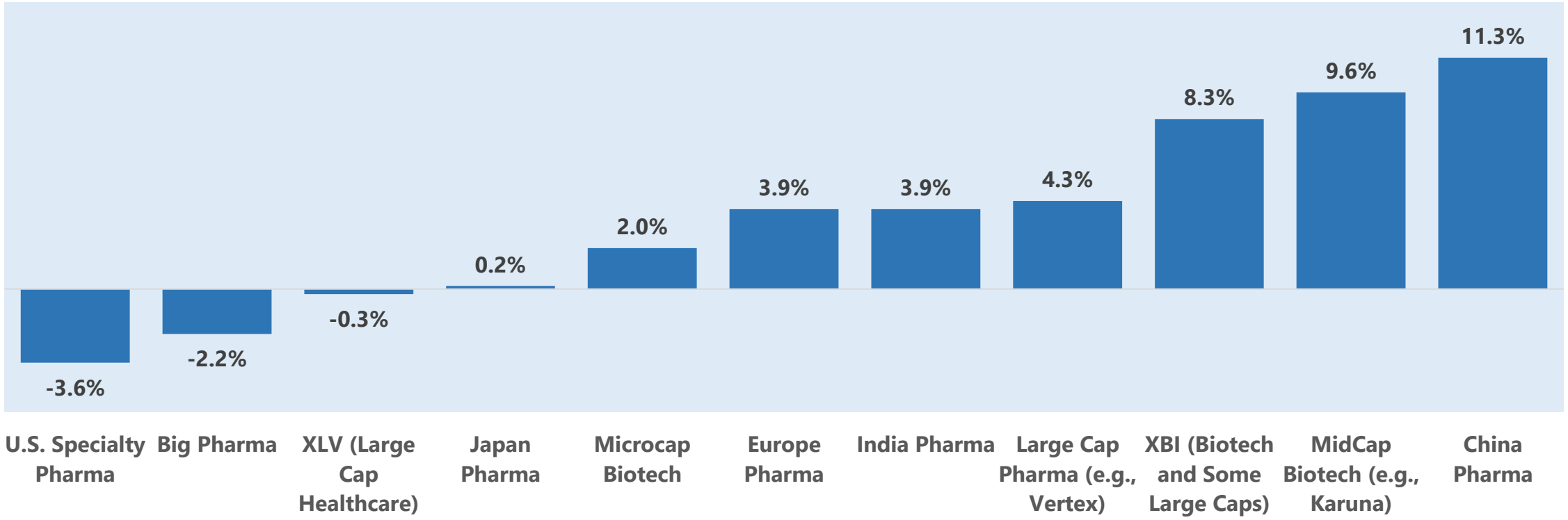
This is a big positive sign.

Source: https://www.institutionalinvestor.com/article/2cgal72ya9j7n17bj394w/premium/casdin-leads-ailing-life-sciences-fund-losses

Where Has the Rally Been Strongest?

The rally in response to the improving macro picture has had the greatest positive effect on China pharma, midcap biotechs and larger commercial pharma (e.g., Alnylam, Vertex). Microcap biotechs have had a positive but modest return while specialty pharma and big pharma have continued to slide. The rally has been uneven and is having the most positive effect on more liquid names. Chinese stocks have, in general, been strong after Beijing has stepped up support of its recently tepid market.

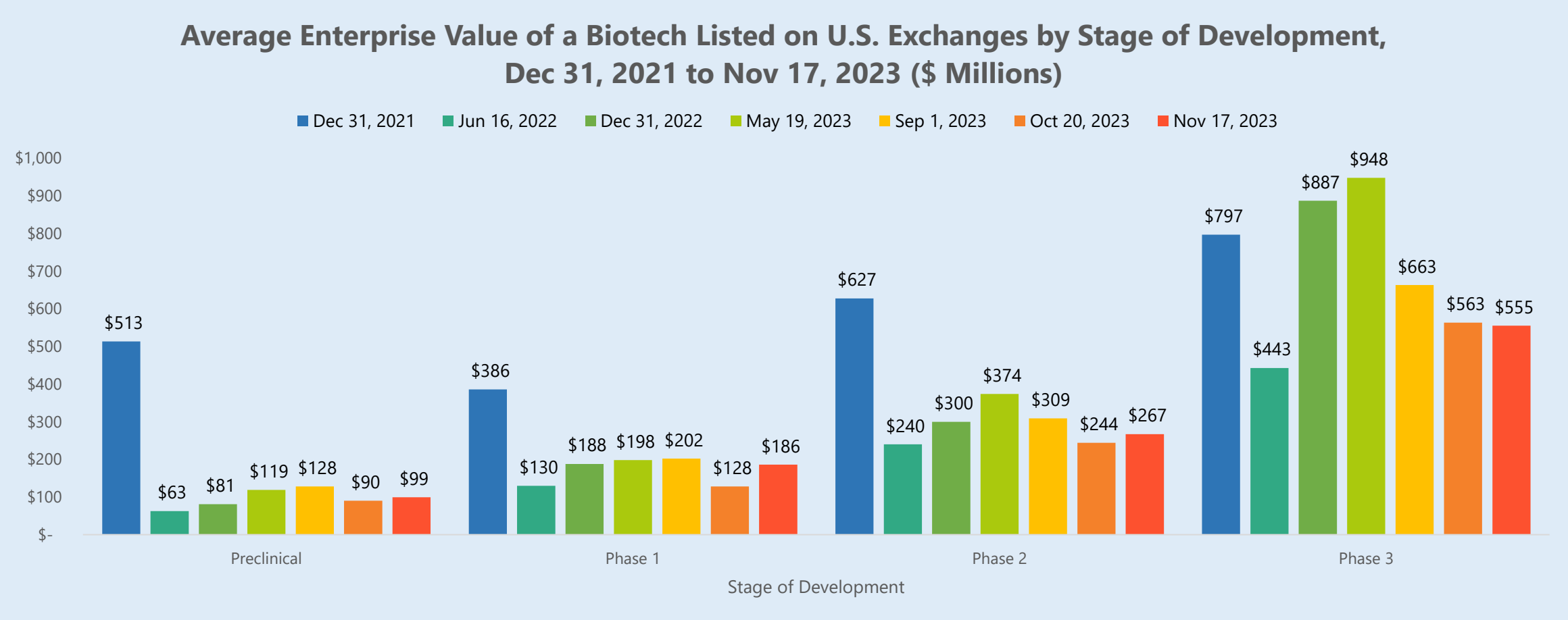
Group Equal-Weighted Share Price Return, October 19 to Nov 17, 2023



Notes: These data are from S&P CapitalIQ and are compiled into equal-weighted indices. Big pharma includes PFE, LLY, MRK, ABBV, NOVO B, ROG, JNJ, AMGN, AZN, NOVN and SAN. China Pharma includes 600276, 1093, 2186, BGNE, 000963, 600196, 000538, 600518, 002422, 000597, 3692 and ZLAB. India Pharma includes SUNPHARMA, 500257, AUROPHARMA, CIPLA, MANKIND, GLENMARK, 500124, ZYDUSLIFE. Europe Pharma includes Merck KGAA, IPN, HLUN A, BAYN, REC, SOBI, ALM, FRE, ORNBV, UCB, GRF. Japan Pharma includes Takeda, Daiichi-Sankyo, Chugai, Astellas, Eisai. Otsuka Holdings, Shionogi, Ono, Kyowa Kirin, Nippon Shinyaku, Santen and Sumitomo Pharma. Large / midcap biotech includes VRTX, ARGX, ALNY, BMRN, INCY, NBIX, OGN, IONS, EXEL, ALKS, ITCI, HRMY, INDV, BPMC, MRTX, SAGE, IDIA, APLS. US Small/midcap pharma includes SUPN, EGRX, CPRX, PCRX, IRWD, JAZZ, COLL, BHC, BLCO, ARQT, HLS, ASRT, OPTN, GTHX, ANIK, HROW, PHAT, ESPR, CALTX, AMARIN, OPK, LQDA, RIGL, EYPT, MRNS, ALIM, TRVN. LargeCap biotech includes KRTX, MDGL, CERE, CYTK, ARWR, PCVX, DNLI, VIR, CRSP, PRTA, BEAM, AKRO, IMVT, VRNA, VTYX, SWTX, SNDX and Microcap biotech includes LCTX, GLSI, GRPH, CYDY, OMER, SVRA, THRD, EVLO, TCRT, CMRX, TSHA, DTIL, OVID, TNYA, VXRT, CUE, XFOR, ATHA, TRVI, CTXR, SELB, CRMD, MTNB, AKBA.

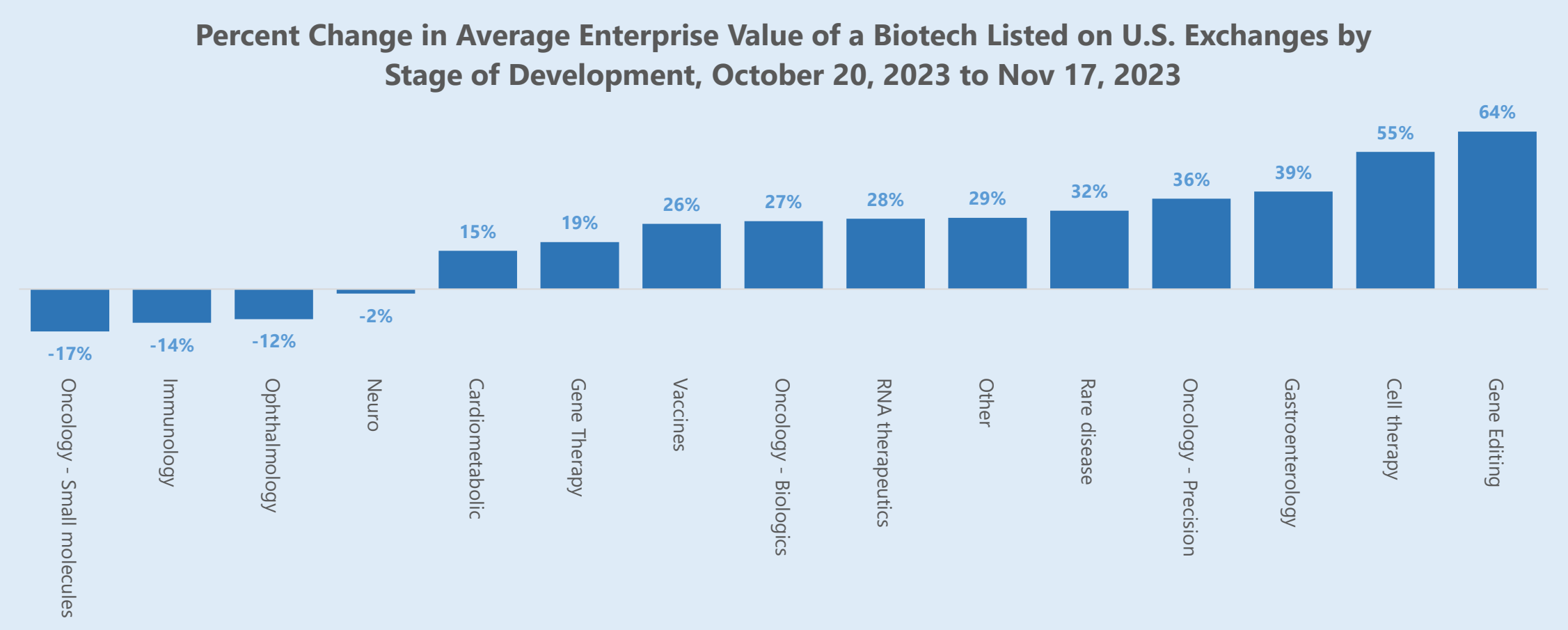
Recent Rally Has Benefitted Early-Stage Biotech the Most

The finding here is a little bit surprising as we have consistently seen a higher premium being paid on later stage assets during the downturn. Now, early-stage companies (particularly Phase 1 and Phase 2) are gaining relative value. In a way, this is intuitive as the rally has been marked by short covering amidst declining rates. Declining rates will benefit long duration companies the most and, presumably, early-stage companies have been more heavily shorted.



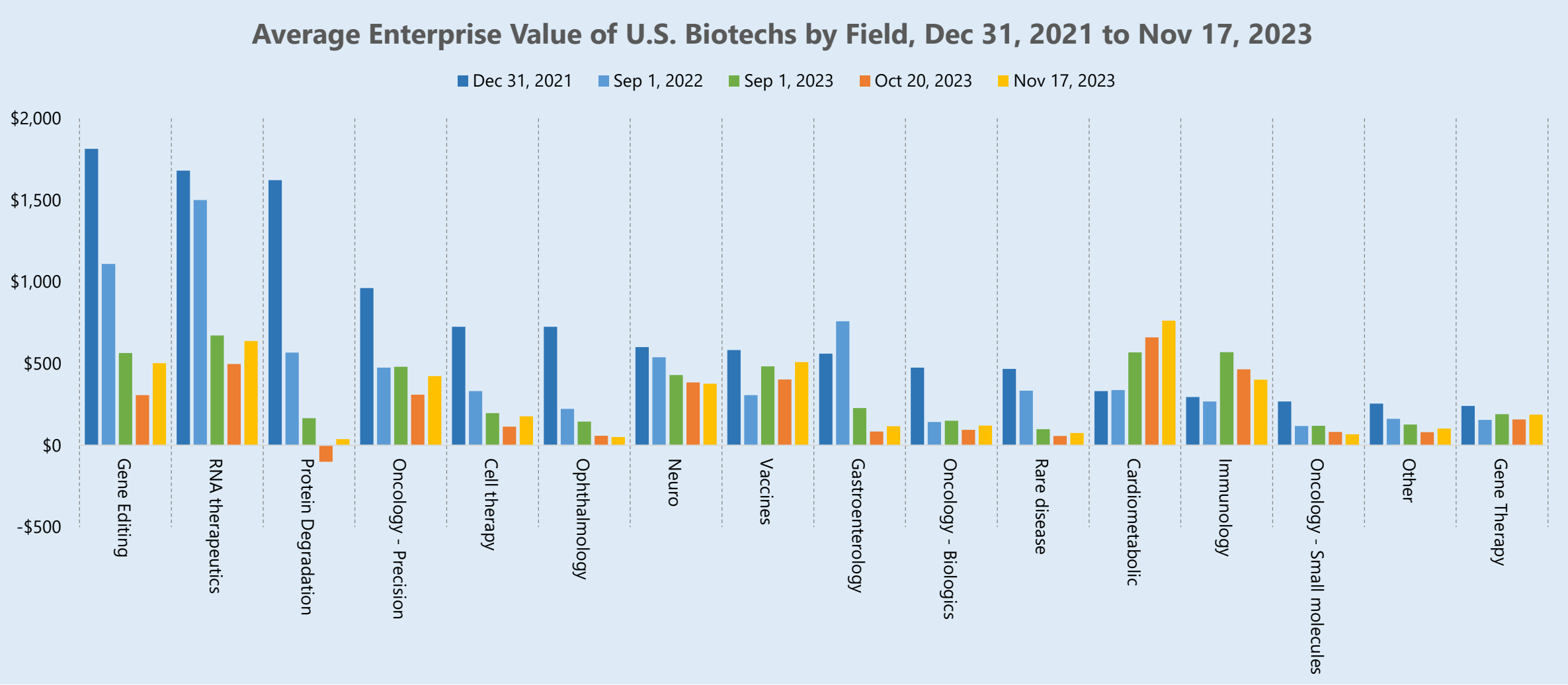
Source: CapitalIQ and Stifel analysis. Phase of development is defined by release of at least some efficacy data from a given stage of clinical development.

Gene Editing, Cell Therapy and Precision Oncology Have Battled Back in Value While Immunology and Small Molecule Oncology Valuations Are Down



Source: CapitalIQ and Stifel analysis.

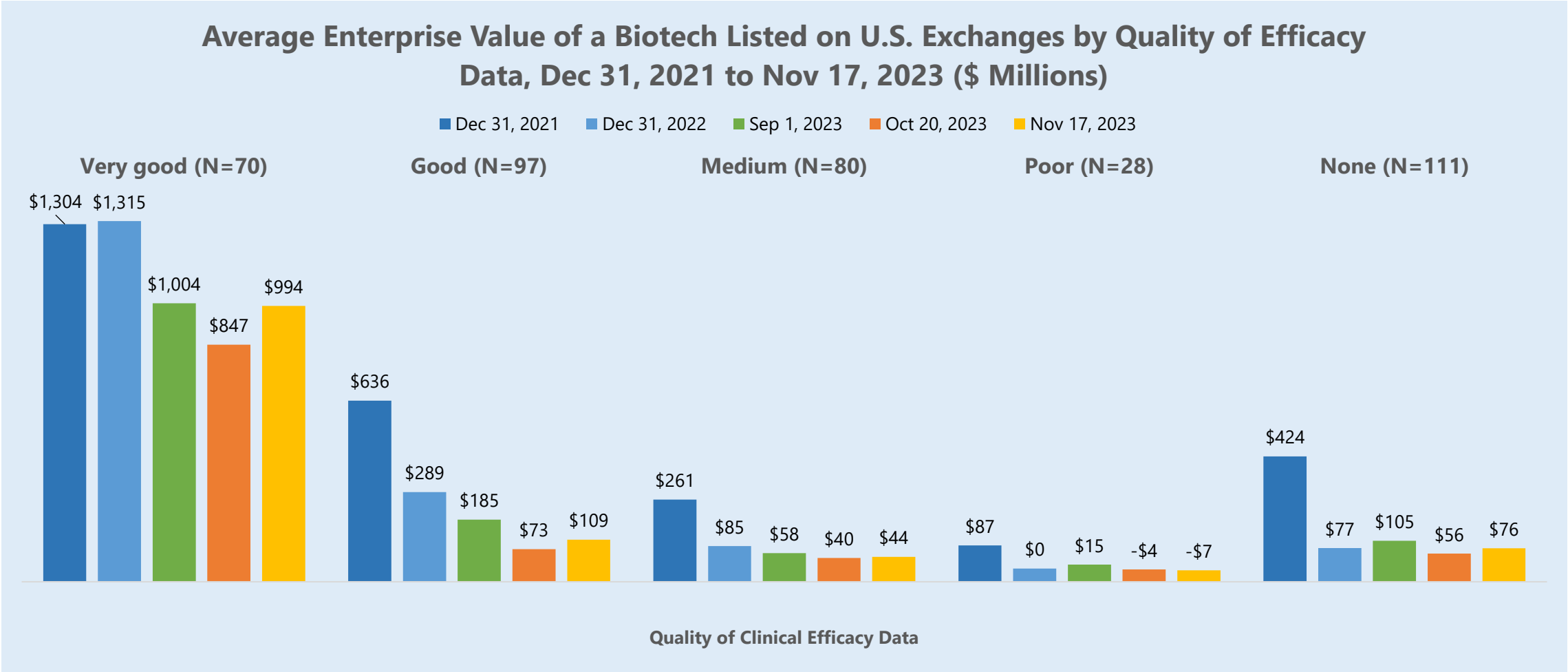
Highest Average US Biotech Valuations Today Found in Cardiometabolic, RNA Therapeutics, Gene Editing and Vaccines



Source: CapitalIQ and Stifel analysis.

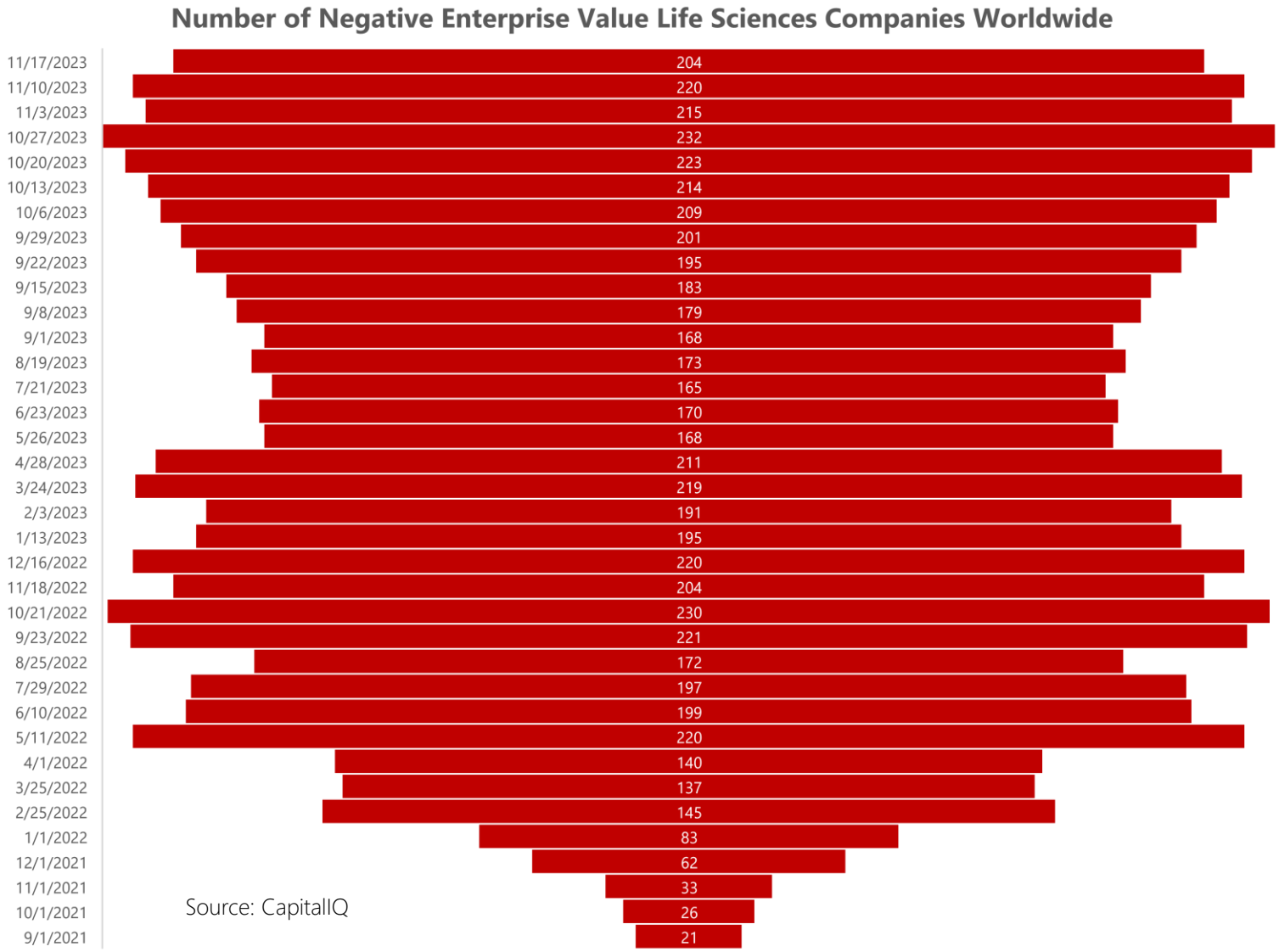
Strong Recovery in Quality Premium in Last Four Weeks

One of the distinctive characteristics of the biotech downturn of 2022 to 2023 has been an extreme quality premium. Companies with "very good" data have traded at a value of five to ten times companies with a "good" dataset. While early-stage companies are coming back in value (a bit) in recent weeks, we are not seeing any meaningful recovery in companies with "medium" or "poor" datasets. If anything, the value of companies with very good and good datasets has gone up while others have not.



Source: CapitalIQ and Stifel analysis.

Number of Negative Enterprise Value Life Sciences Companies Fell to 204 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide fell from 220 a week ago to 204 last Friday.

Life Sciences Sector Up 2.7% Last Week

Last week saw a 2.7% rise in life sciences stocks worldwide. The sector's value rose by $225 billion. Biotech and diagnostics stocks were up the most. Also, devices and tools stocks did well.

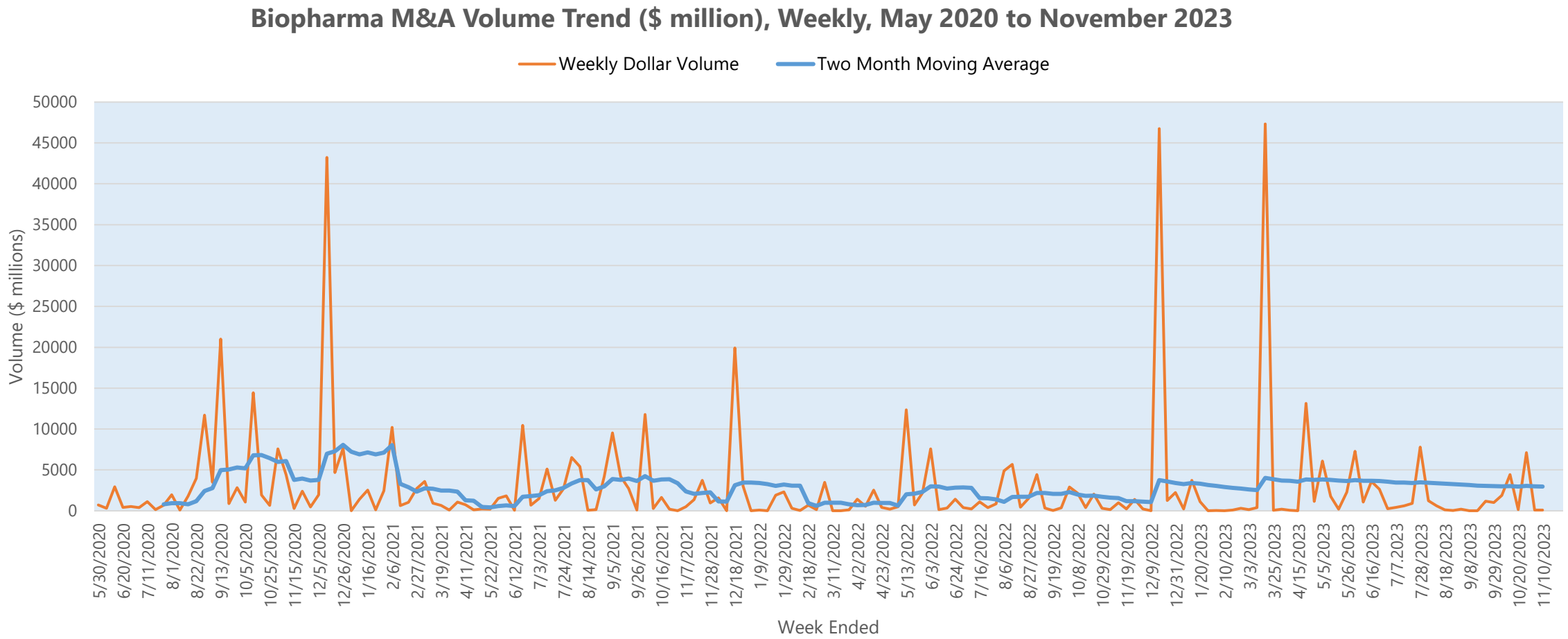
Sector	Firm Count	Enterprise Value (Nov 17, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$83,076	1.2%	6.4%	-1.9%
Biotech	812	$172,972	9.8%	17.9%	-5.1%
CDMO	40	$153,214	2.5%	3.2%	-14.1%
Diagnostics	83	$247,967	7.8%	11.7%	-4.7%
OTC	31	$27,607	-0.1%	-0.2%	-1.1%
Pharma	724	$5,676,184	1.5%	0.0%	-0.9%
Services	39	$202,363	1.5%	5.2%	1.7%
Tools	53	$605,130	4.0%	-1.1%	-19.4%
Devices	181	$1,502,741	5.3%	4.0%	-2.4%
HCIT	11	$21,381	2.5%	-3.1%	-25.5%
Total	**2055**	**$8,694,536**	**2.7%**	**1.4%**	**-3.2%**

Source: CapitalIQ

Deals Environment Update

M&A Market Active Last Week

Last week saw two proposals by Japanese companies to acquire life science companies, including Astellas' agreement to acquire Propella Therapeutics for $175 million and Ajinimoto's proposal to buy Forge Biologics, a cell and gene therapy CDMO, for $620 million. Also, Graphite agreed to acquire Lenz, Selecta agreed to merge with Cartesian Therapeutics and Homology agreed to merge with Q32. This was the most active week for reverse mergers in the history of the life sciences industry.



Source: S&P, CapitalIQ

Ajinomoto to Buy Forge Biologics for $620 Million

COLUMBUS, Ohio, November 13, 2023 – Ajinomoto Co., Inc. ("Ajinomoto Co."; TYO: 2802) and Forge Biologics (Forge), announced today that they have entered into a definitive agreement by which Ajinomoto Co., will acquire Forge, a leading manufacturer of genetic medicines, in an all-cash deal for $620 million1.

Forge is a viral vector and plasmid contract development and manufacturing organization (CDMO) and clinical-stage therapeutics company, enabling access to potentially life-changing gene therapies by bringing them from concept to reality. All development and manufacturing is done at the Hearth, Forge's 200,000 square foot custom-designed cGMP facility in Columbus, Ohio, where the business has over 300 employees.

"Forge has had remarkable growth since our founding in 2020, and we're excited to join Ajinomoto Co., to continue to expand our global business of helping innovators manufacture much needed genetic medicines," said Timothy J. Miller, Ph.D., CEO, President, and Co-founder of Forge. "Our teams share a commitment to investing in innovation that helps our clients succeed in delivering therapies to patients in need. We set out to build a company with a mission to enable access to life-changing discoveries, and this transaction will support us in advancing that mission into our next global stage of development to expand our capabilities and platform for the benefit of our clients and their patients."

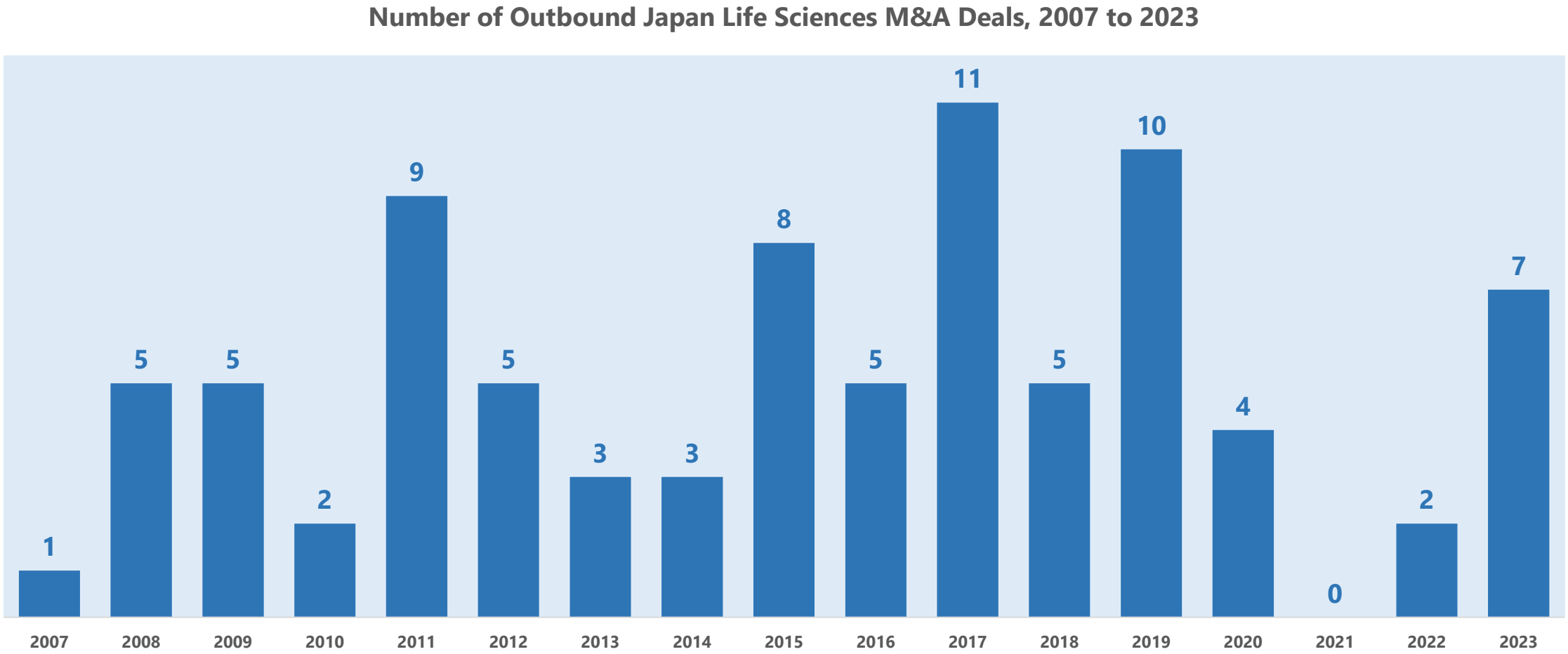
"Forge's unparalleled expertise in gene therapy development and manufacturing will be a transformative addition to our core growth area of Healthcare as part of our ASV Initiatives 2030 Roadmap. Forge brings to Ajinomoto an entirely new capability that will vitally enhance our Bio-Pharma Services business and help create new value through innovative solutions for communities and society," said Yasuyuki Otake, Corporate Executive, General Manager of Bio-Pharma Services Department of Ajinomoto Co. "We look forward to working with Forge's incredibly talented team and state-of-the-art specialized manufacturing facility to expand our platform technologies aimed to help realize Ajinomoto's 'Purpose' of contributing to the well-being of all human beings, our society, and our planet."

"This is a tremendous step to drive Forge's next phase of growth that will maximize the impact they have on their mission for clients and patients," said Chris Garabedian, Chairman and CEO of Xontogeny and Chairman of Forge's Board of Directors. "This acquisition in the current biotech market is a remarkable testament to the technical advancements, world-class facility, and experienced capable leadership at Forge."

Source: https://www.forgebiologics.com/ajinomoto-co-inc-to-acquire-forge-biologics-for-620-million1/

Japan M&A Has Picked Up Substantially in 2023

After quieting down substantially in 2021 and 2022, Japan life sciences M&A activity has bounced back to historic levels in 2023.



Source: DealForma

Q32 Bio and Homology Medicines Announce Merger Agreement

WALTHAM, Mass. and BEDFORD, Mass., Nov. 16, 2023 (GLOBE NEWSWIRE) - Q32 Bio Inc., a clinical stage biotechnology company developing biologic therapeutics to restore immune homeostasis, and Homology Medicines, Inc. (Nasdaq: FIXX), today announced they have entered into a definitive merger agreement to combine the companies in an all-stock transaction. The combined company will focus on advancing Q32 Bio's wholly owned clinical development candidates for the treatment of autoimmune and inflammatory diseases. Upon completion of the merger, the combined company will operate as Q32 Bio, headquartered in Waltham, Massachusetts, and is expected to trade under the Nasdaq ticker symbol "QTTB".

In support of the merger agreement, Q32 Bio has entered into an agreement for a $42 million private placement with participation from existing and new investors including OrbiMed, Atlas Venture, Abingworth, Bristol Myers Squibb, Acorn Bioventures, Osage University Partners (OUP), CU Healthcare Innovation Fund, Sanofi Ventures, Agent Capital and other undisclosed investors.

"The proposed merger with Homology Medicines and concurrent private placement is expected to provide Q32 Bio with the capital to drive development of our autoimmune and inflammatory pipeline through multiple clinical milestones," said Jodie Morrison, Chief Executive Officer of Q32 Bio. "This funding is expected to enable us to deliver two Phase 2 readouts for bempikibart in the second half of 2024, proof-of-concept data for ADX-097, a tissue-targeted inhibitor of complement activation, by year-end 2024, and topline ADX-097 clinical results in the second half of 2025."

Proceeds from the proposed transactions will be used to advance the clinical development of Q32 Bio's two wholly owned assets, bempikibart (ADX-914), for which Q32 Bio earlier today announced it regained all rights from Amgen, and ADX-097.

Bempikibart, Q32 Bio's lead program, is a fully human anti-IL-7Rα antibody that re-regulates adaptive immune function by blocking signaling mediated by both IL-7 and TSLP and is currently being evaluated in two Phase 2 trials, with one clinical trial evaluating the use in atopic dermatitis (AD) and one evaluating the use in alopecia areata (AA). All data from the Phase 2 trials remain blinded and Q32 Bio remains on track to report topline Phase 2 results in the second half of 2024.

Source: https://investors.homologymedicines.com/news-releases/news-release-details/q32-bio-and-homology-medicines-announce-merger-agreement

LENZ Therapeutics and Graphite Bio Announce Merger Agreement

SAN DIEGO & SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE) – November 15, 2023 - LENZ Therapeutics, a late-stage biopharmaceutical company focused on developing and commercializing innovative therapies to improve vision, and Graphite Bio, Inc. (NASDAQ: GRPH) today announced that they have entered into a definitive merger agreement to combine the companies in an all-stock transaction. The lead programs of the combined company will address presbyopia, the inevitable loss of near vision that impacts the daily lives of nearly all people over the age of 45. The combined company is expected to trade on Nasdaq under the ticker symbol "LENZ."

In connection with the merger, Graphite Bio has entered into a subscription agreement for a PIPE financing that is expected to close concurrently with the completion of the merger of $53.5 million, with a syndicate of healthcare investors led by LENZ's existing investors and including participation from new investors. The merger is subject to stockholder approval of both companies, the effectiveness of a registration statement to be filed with the U.S. Securities and Exchange Commission to register the securities to be issued in connection with the merger, and the satisfaction of customary closing conditions.

With the cash expected from both companies at closing and the proceeds of the concurrent PIPE financing, the combined company is expected to have approximately $225 million of cash or cash equivalents. Graphite Bio is expected to contribute $115 million to the combined entity and expects to pay a dividend to Graphite Bio shareholders of approximately $60 million at the close of the transaction. Upon close, key healthcare investors in the combined company will include Versant Ventures, RA Capital Management, Alpha Wave Global, Point72, Samsara BioCapital, Sectoral Asset Management, RTW Investments and others. It is expected that the net proceeds from the merger and concurrent financing will allow the combined company to continue to build infrastructure and successfully commercialize LENZ's lead product candidate, subject to successful completion of the ongoing Phase 3 trials, New Drug Application (NDA) submission and subsequent FDA approval.

"I am pleased to announce our merger with Graphite Bio, allowing us to create a publicly traded company focused on the advancement of LENZ's lead programs, LNZ100 and LNZ101 for the treatment of presbyopia. This pivotal change comes at an important time for the company as we gear up for the readout of the Phase 3 CLARITY trials in the second quarter of 2024," said Eef Schimmelpennink, President and CEO of LENZ Therapeutics. "We believe that a once-daily pharmacological eye drop that can effectively and safely improve near vision throughout the full workday, without the need for reading glasses, will be a highly attractive commercial product with an estimated U.S. market opportunity in excess of $3 billion. We have assembled an executive team with extensive clinical, commercial and operational experience to commercialize such a product and become the category leader."

Source: https://www.businesswire.com/news/home/20231115881807/en/LENZ-Therapeutics-and-Graphite-Bio-Announce-Merger-Agreement

Selecta Biosciences Announces Merger with Cartesian Therapeutics

WATERTOWN, Mass. and GAITHERSBURG, Md., Nov. 13, 2023 (GLOBE NEWSWIRE)—Selecta Biosciences, Inc. (NASDAQ: SELB) (the Company) today announced that it has merged with Cartesian Therapeutics, Inc., a clinical-stage biotechnology company pioneering RNA cell therapies for autoimmune diseases. In connection with the merger, Selecta announced a $60.25 million private financing led by Timothy A. Springer, Ph.D., member of the Selecta Board of Directors.

With the cash from both companies at closing and the proceeds of the concurrent private financing, the combined company is expected to have over $110 million on hand to support the development of the Cartesian pipeline through the Phase 3 study of lead product candidate, Descartes-08, a potential first-in-class RNA-engineered chimeric antigen receptor T-cell therapy (rCAR-T) for the treatment of MG, as well as the advancement of additional RNA cell therapy programs.

"We are thrilled to announce our merger with Cartesian, a true pioneer in the RNA cell therapy space," said Carsten Brunn, Ph.D., who will continue to serve as President and Chief Executive Officer of the combined company. "With several potential value-driving milestones expected in the near-term, including data from the ongoing Phase 2b study of Descartes-08 in MG expected in mid-2024, we are confident that this merger represents a significant opportunity for Selecta stockholders. Cartesian's mission aligns seamlessly with Selecta's commitment to advancing innovative therapies for the treatment of autoimmune diseases, and we look forward to working toward maximizing the potential of this robust pipeline and technology."

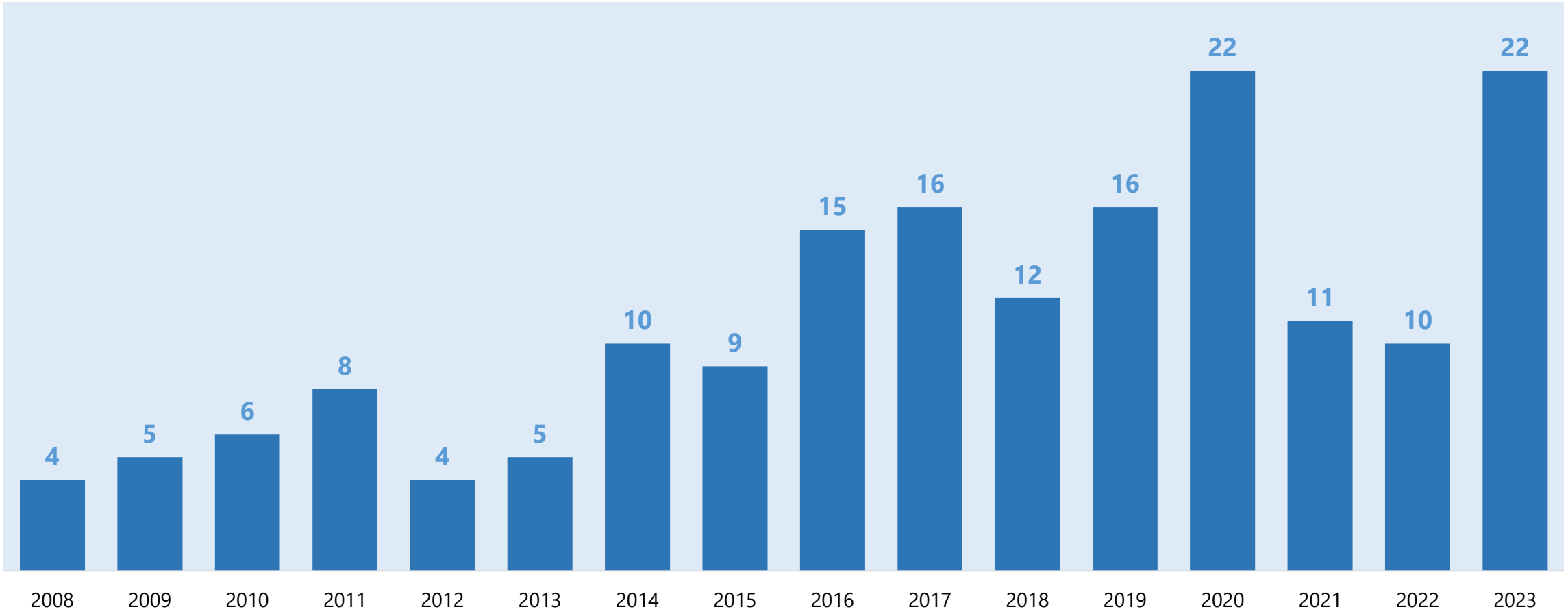
"RNA cell therapy has the potential to overcome the challenges of using conventional, costly DNA-engineered cell therapies to treat autoimmune diseases, including their toxicity and the need for preconditioning chemotherapy," said Murat Kalayoglu, M.D., Ph.D., Co-Founder and former Chief Executive Officer of Cartesian. "With a shared vision of bringing meaningful therapeutic options to patients with autoimmune diseases, we are confident that our novel approach can thrive under Carsten's leadership."

Source: https://ir.selectabio.com/news-releases/news-release-details/selecta-biosciences-announces-merger-cartesian-therapeutics

Reverse Merger Activity at Record Levels in 2023

The three reverse merger announcements last week have helped to push 2023 close to the record books for biotech reverse mergers (and there remains another six weeks to go in the year). The absence of an open IPO window has encouraged many quality companies to take the reverse route this year.

Number of Biotech Reverse Mergers Announced by Year, 2008 to 2023



Source: DealForma and Stifel reverse merger database

Record Number of Biopharma Companies Exploring Strategic Options

By our count, there are 47 biopharma companies that have indicated that they are exploring strategic alternatives or are going through an sale process for assets via a bankruptcy or liquidation. This is an all-time record based on the statistics that we keep.

Ticker	Company	Note	Announcement Date	Last Cash ($mm)	Enterprise Value ($mm)
TMBR	Timber Pharma	BK	11/17/2023	$2.5	$2.5
BCEL	Atreca		11/16/2023	$21.4	-$11.5
THRX	Theseus		11/14/2023	$205.1	-$71.0
KTRA	Kintara Therapeutics		10/31/2023	$0.2	$11.0
LIAN	LianBio		10/24/2023	$252.2	$232.9
EVLO	Evelo Biosciences		10/17/2023	$17.3	$26.1
ATHX	Athersys		10/16/2023	$1.0	$18.7
RAIN	Rain Oncology	AC	10/16/2023	$77.3	-$36.9
IMPL	Impel Pharmaceuticals	BK	10/5/2023	$0.2	$122.0
GLTO	Galecto		9/26/2023	$44.2	-$27.1
ARAV	Aravive		8/21/2023	$8.5	$3.4
GRTX	Galera Therapeutics		8/14/2023	$28.4	$130.9
TCRT	Alaunos Therapeutics		8/14/2023	$11.9	$5.4
SLRX	Salarius Pharmaceuticals		8/8/2023	$7.6	-$4.4
NBSE	Neubase		8/3/2023	$13.8	-$4.8
AVTX	Avalo Therapeutics		8/3/2023	$10.2	$9.1
VXL	Vaxil Bio		8/2/2023	$0.7	$0.3
SQZB	SQZ Biotechnologies		7/25/2023	$10.2	$11.9
ELYM	Eliem Therapeutics		7/20/2023	$107.4	-$36.9
RKDA	Arcadia Biosciences		7/20/2023	$15.7	-$11.2
NMTR	9 Meters	BK	7/19/2023	$0.0	$0.0
PIRS	Pieris Pharma		7/18/2023	$44.8	-$10.2
AVRO	AvroBio		7/12/2023	$105.8	-$46.6

Source: Stifel Research. Note: BK means in bankruptcy, AC means activist present and LQ means in liquidation.

Ticker	Company	Note	Announcement Date	Last Cash	Enterprise Value
HSTO	Histogen	LQ	7/5/2023	$4.6	-$4.2
RVLP.Q	RVL Pharmaceuticals		7/5/2023	$19.2	$39.5
SPEX	Spexis		6/30/2023	$1.0	$9.9
AUPH	Aurinia Pharma	AC	6/29/2023	$337.1	$991.2
BLPH	Bellorophon tX		6/24/2023	$4.4	-$4.0
ONSC	Oncosec	BK	6/14/2023	$0.3	$0.0
ONCR	Oncorus		6/1/2023	$45.0	$24.8
NOVN	Novan	BK	5/31/2023	$12.5	$24.2
GMDA	Gamida Cell		5/15/2023	$60.4	$65.5
IMVI.Q	IMV	BK	5/1/2023	$21.2	$7.7
INFI	Infinity Pharma	BK	3/28/2023	$0.4	$0.7
BLCM	Bellicum Therapeutics		3/14/2023	$5.9	$27.3
FRTX	Fresh Tracks Thx		3/7/2023	$12.0	-$7.1
EVFM	Evofem Biosciences		2/23/2023	$7.7	$81.0
GTTX	Genetether		2/8/2023	$2.0	$1.0
AXLA	Axcella Therapeutics		12/14/2022	$8.9	$8.5
MEIP	MEI Pharma	AC	12/6/2022	$82.2	-$29.7
SNGX	Soligenix		11/10/2022	$17.0	$4.0
HGEN	Humanigen		10/31/2022	$3.1	-$3.0
XCUR	Exicure		9/26/2022	$15.6	-$3.0
TENX	Tenax Therapeutics		9/14/2022	$11.1	-$1.9
GLMD	Galmed		6/15/2022	$22.4	-$12.0
ABIO	Arca Bio	AC	4/18/2022	$43.9	-$12.0
ADMA	ADMA Biologics		10/21/2021	$74.2	$975.9

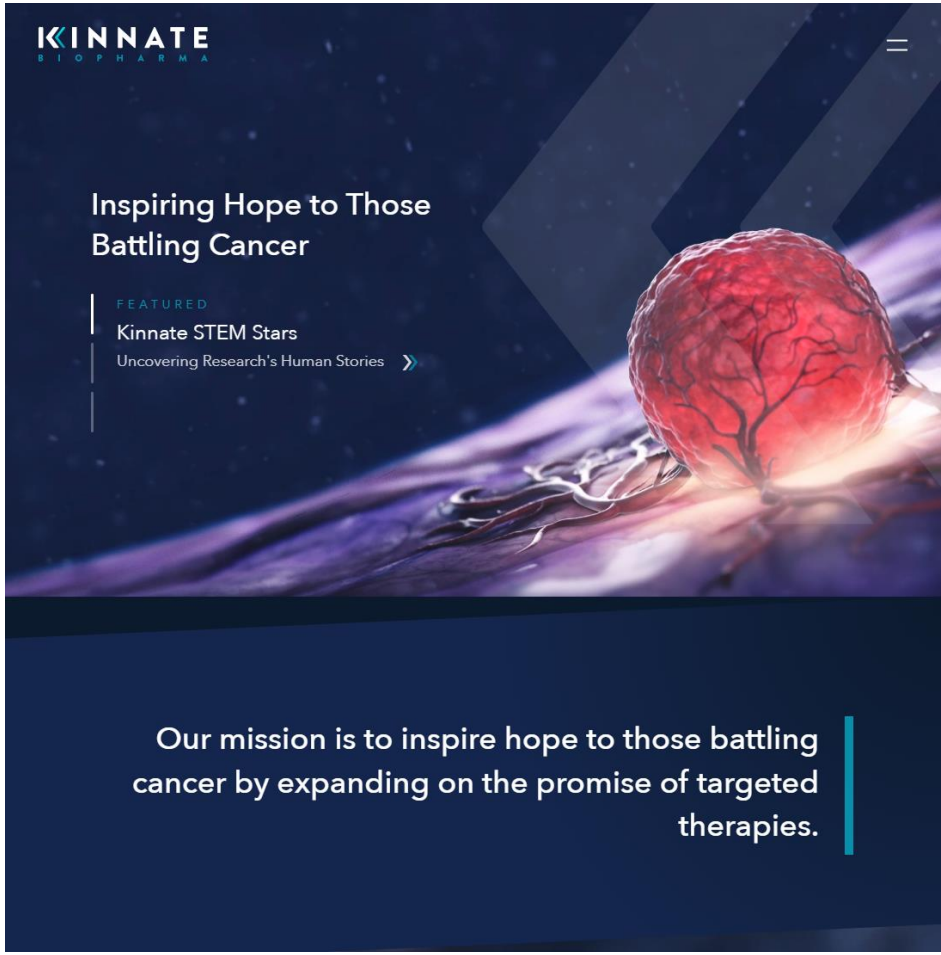
Kinnate Biopharma Receives Exploratory Interest to Take the Company Private

8-K Filing

On November 13, 2023, the board of directors (the “Board”) of Kinnate Biopharma Inc. (the "Company") received a letter from funds affiliated with Foresite Capital Management, LLC (collectively, “Foresite”) and funds affiliated with OrbiMed Advisors LLC (collectively, “OrbiMed”) in which Foresite and OrbiMed indicated their intent to explore and evaluate a potential acquisition of all of the outstanding shares of common stock of the Company not already owned by Foresite or OrbiMed in a going-private transaction.

The Board will carefully consider any proposal that is presented by Foresite and OrbiMed in accordance with the Board’s fiduciary duties and with the same care and attention it would consider other similar proposals if received by the Company.

Kinnate Biopharma was trading at one of third of its cash level prior to the interest from inside shareholders and is now trading at two thirds of its cash level. Go private transactions have not been unusual in 2023 in biotech because companies are trading at such depressed valuations.



Source: https://www.sec.gov/ix?doc=/Archives/edgar/data/0001797768/000114036123053357/ef20014753_8k.htm

Timber Pharmaceuticals Files for Chapter 11 After Shareholders Vote Down Merger

Josh Beckerman, *Wall Street Journal*, November 17, 2023 (excerpt)

Timber Pharmaceuticals filed for chapter 11 bankruptcy protection on a day when LEO Pharma terminated a merger agreement that didn't receive a sufficient stockholder vote at a Friday meeting.

Timber signed a stalking-horse asset-sale agreement with LEO Pharma.

Timber, which focuses on treatments for rare and orphan dermatologic diseases, previously warned that there was substantial doubt about its ability to continue as a going concern and said it would "likely need to seek the protection of the bankruptcy courts" if the merger wasn't completed.

The company adjourned its stockholder meeting on Oct. 16 and again on Oct. 30.

Before a trading halt earlier on Friday, Timber shares were up 17%, to $1.46. On the day the LEO Pharma deal was announced in August, Timber shares closed at $2.99, up from $1.42 in the previous session.

Source: https://www.wsj.com/business/timber-pharmaceuticals-files-for-chapter-11-5ba1e9bb

Legend Biotech Announces Exclusive, Global License Agreement for Certain CAR-T Therapies Targeting DLL3

SOMERSET, N.J.— NOVEMBER 13, 2023—Legend Biotech Corporation (NASDAQ: LEGN) (Legend Biotech), a global biotechnology company developing, manufacturing and commercializing novel therapies to treat life-threatening diseases, announced today that Legend Biotech Ireland Limited, a wholly owned subsidiary of Legend Biotech, has entered into an exclusive, global license agreement (License Agreement) with Novartis Pharma AG for certain Legend Biotech chimeric antigen receptor T-cell (CAR-T) cell therapies targeting DLL3, including its autologous CAR-T cell therapy candidate, LB2102 (NCT05680922).[i] The License Agreement grants Novartis the exclusive worldwide rights to develop, manufacture and commercialize these cell therapies, and Novartis may apply its T-Charge™ platform to their manufacture.

Under the License Agreement, Legend Biotech will conduct a Phase 1 clinical trial for LB2102 in the U.S. Novartis will conduct all other development for the licensed products.

Under the terms of the License Agreement, Legend Biotech will receive a $100 million upfront payment and will be eligible to receive up to $1.01 billion in clinical, regulatory and commercial milestone payments and tiered royalties. Closing of the transaction is subject to the parties' receipt of any necessary consents or approvals, including the expiration or termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

Source: https://legendbiotech.com/legend-news/legend-biotech-announces-exclusive-global-license-agreement-for-certain-car-t-therapies-targeting-dll3/

Kite and Arcellx Announce Expansion in Strategic Partnership

November 15, 2023 - SANTA MONICA, Calif. & REDWOOD CITY, Calif.--(BUSINESS WIRE)-- Kite, a Gilead Company (NASDAQ: GILD), and Arcellx, Inc. (NASDAQ: ACLX), today announced that the companies have expanded their existing collaboration, which was originally announced in December 2022.

Kite has exercised its option to negotiate a license for Arcellx's ARC-SparX program, ACLX-001, in multiple myeloma, which is comprised of ARC-T cells and SparX proteins that target BCMA. The companies have also expanded the scope of the collaboration for Arcellx's CART-ddBCMA to include lymphomas.

"We are pleased to see the momentum with the CART-ddBCMA multiple myeloma program, enabling Kite to enter an area of high unmet need and bring a new, potentially best-in-class cell therapy to patients," said Cindy Perettie, Executive Vice President of Kite. "Given this, we are deepening our relationship with Arcellx to further support advancement of CART-ddBCMA, bolster our pipeline in multiple myeloma, as well as access opportunities in lymphoma. In expanding our strategic partnership with Arcellx, we are building upon the established synergy between Arcellx's platform technologies and Kite's industry-leading position in CAR T manufacturing and commercialization."

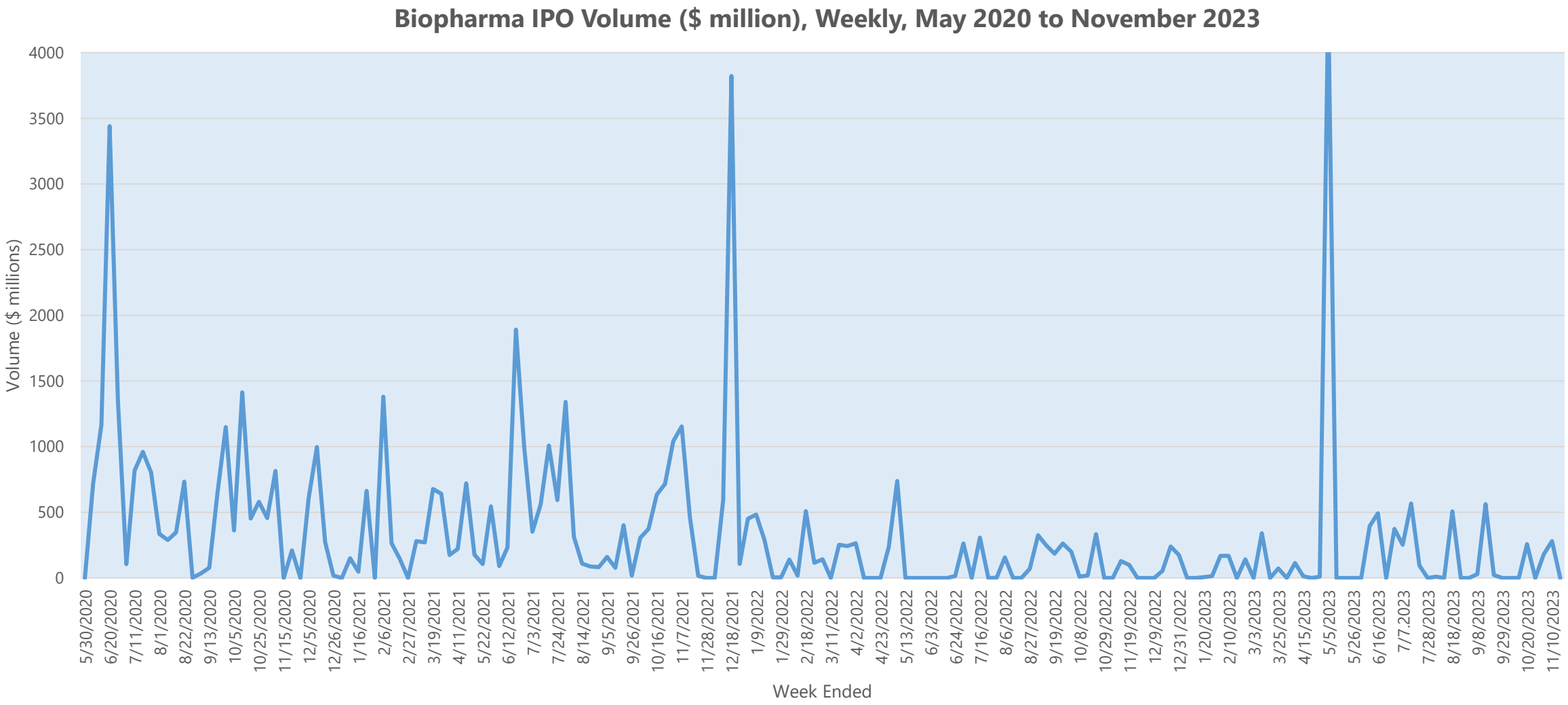
ARCELLX

Arcellx to receive $200M equity investment at $61.68 per share and an $85 million upfront cash payment in a stock / cash deal that is typical of other Gilead deals.

Source: https://www.gilead.com/news-and-press/press-room/press-releases/2023/11/kite-and-arcellx-announce-expansion-in-strategic-partnership

Capital Markets Update

IPO Market Saw No Transactions Last Week



Source: Data from CapitalIQ and Stifel research.

Alkermes Oncology Completed Spin of Mural Oncology Last Week

DUBLIN, Nov. 15, 2023 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced that it has completed the separation of its oncology business into Mural Oncology plc (Mural Oncology), a new, independent, publicly traded company. Alkermes is now a pure-play, profitable neuroscience company that will continue its work to develop innovative medicines for people living with difficult-to-treat psychiatric and neurological disorders. Mural Oncology will begin "regular way" trading on the Nasdaq Global Market under the stock ticker symbol "MURA" on Nov. 16, 2023. Alkermes will continue to trade under the Nasdaq ticker symbol "ALKS." "The separation of our oncology business was an important element of our strategy to transform Alkermes into a pure-play neuroscience company with the potential to generate strong profitability and cash flow. With a topline driven by the growth of our proprietary commercial products, proven drug development capabilities, and an important pipeline opportunity in our ALKS 2680 orexin program, we believe we are well positioned to drive value for Alkermes shareholders," said Richard Pops, Chief Executive Officer of Alkermes.

Source: https://investor.alkermes.com/news-releases/news-release-details/alkermes-completes-separation-oncology-business

Mural Oncology Focused on a Phase 3 IL-2 Variant

Nemvaleukin: A Disciplined and Systematic Approach to Developing an Engineered IL-2 Variant

Development Stage Gates

Novel Design

- Fusion protein of IL-2 and IL-2Rα, designed to expand the therapeutic benefits of high-dose recombinant human IL-2 (rhIL-2) while mitigating its hallmark toxicities
- Stable, intrinsically active without the need for metabolic or proteolytic conversion

Nemvaleukin

Pharmacological PoC

- Dose-dependent expansion of NK and $CD8^+$ T cells
- Minimal non-dose dependent effects on T_{regs}

Clinical Validation

- Monotherapy responses observed in melanoma and RCC in patients previously treated with a CPI
- Observed responses in combination with pembrolizumab
- IV QDx5 every 3 weeks dosing modeled after high dose IL-2

Potential Approval and Indication Expansion

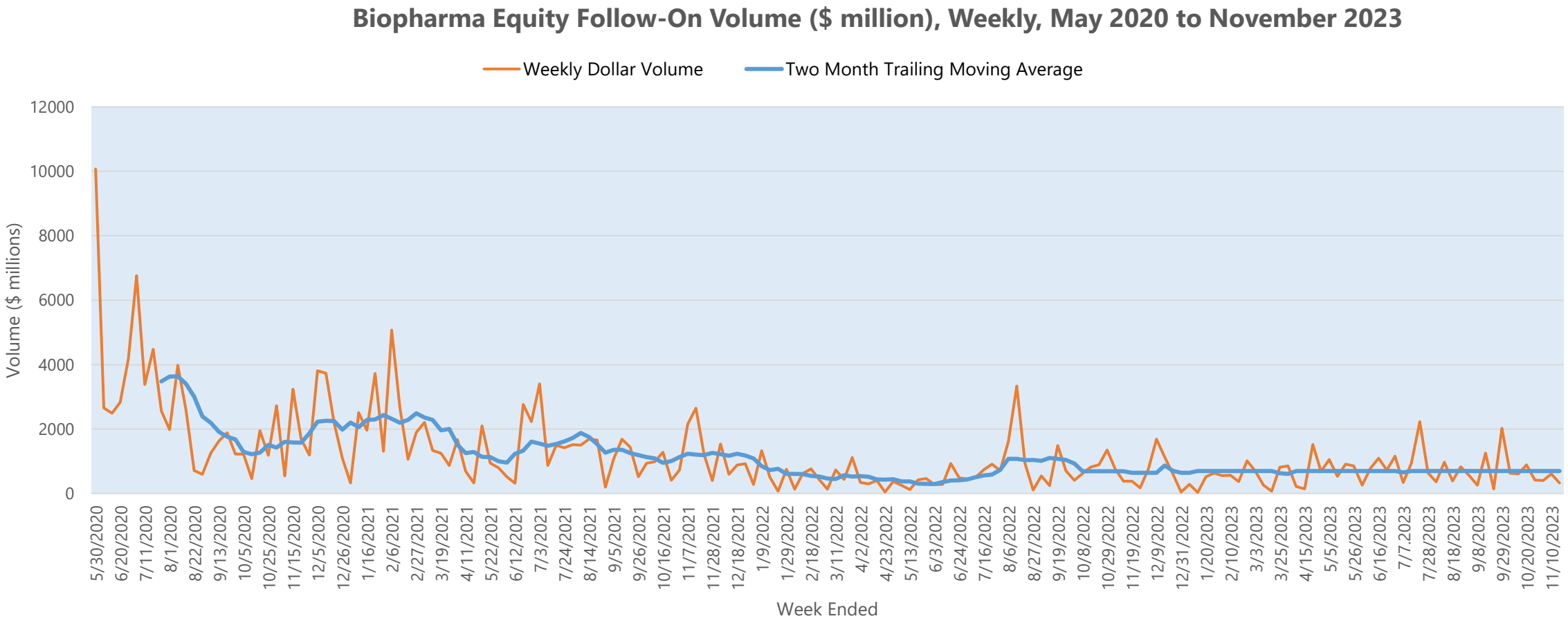
- Two near-term potentially registrational data readouts
  - PROC: FDA Fast Track designation
  - Mucosal Melanoma: FDA Fast Track designation and Orphan Drug designation. Focus on additional dosing approaches, including less frequent IV dosing regimens
- Potential for indication expansion

12 Abbrev: **RCC**: Renal Cell Carcinoma; **CPI:** Checkpoint Inhibitor; **FDA**: Food and Drug Administration; **IL-2R**: IL-2 receptor; **rhIL-2:** recombinant human IL-2; **IL-2Rα:** IL-2R alpha

MURAL ONCOLOGY

Last Week Was Quite Slow for Follow-On Offerings

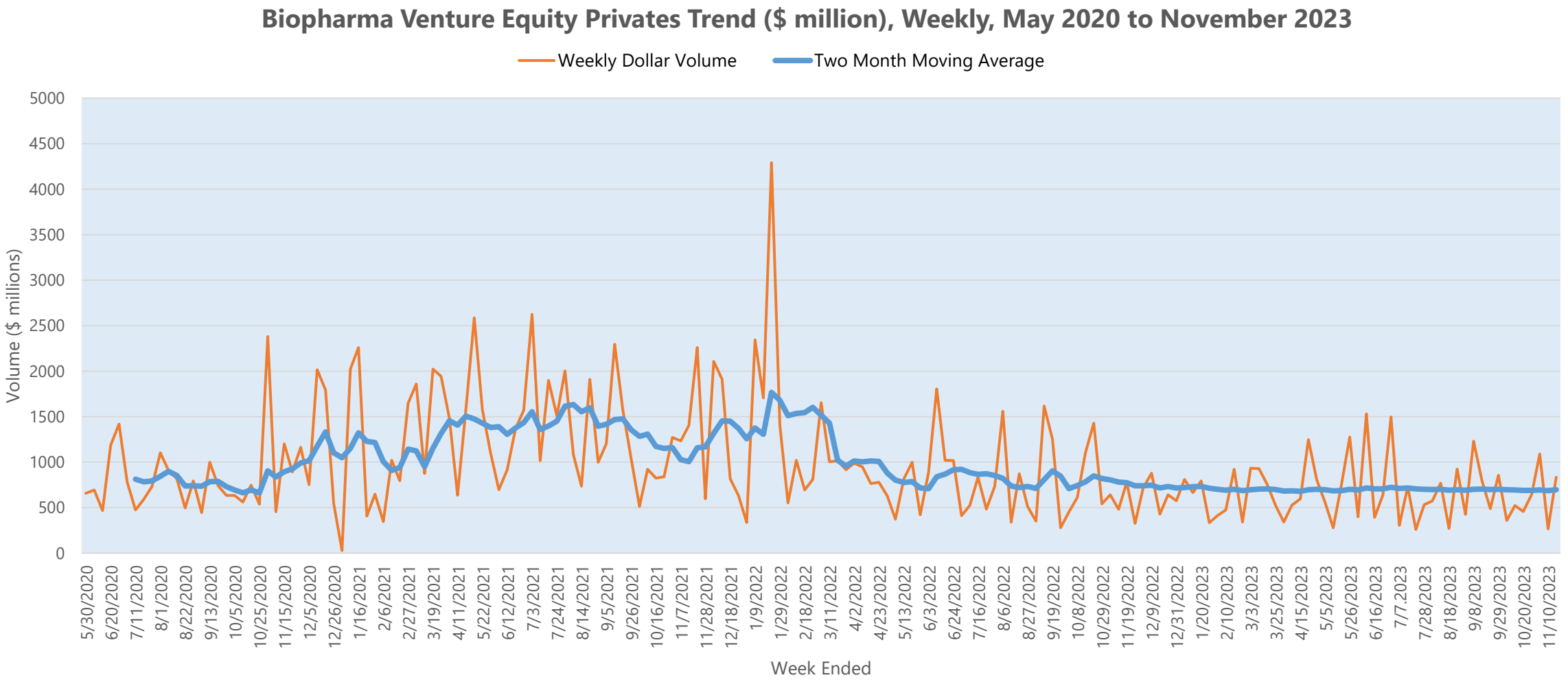
Last week saw very light follow-on offering as the market remained in some disarray. The main issuances that took place came from PIPE's associated with reverse mergers and a PIPE by Gilead into Arcellx. If one excludes these deals there was only $11mm in volume in the market.



Source: Data from CapitalIQ and Stifel research.

Venture Equity Market Picked Up Last Week

Last week was relatively active in the venture equity market with $833mm of deals. Key fundraisers included VectorY and Mbrace.



Source: Data from CapitalIQ, Crunchbase.

VectorY Raises €129 Million ($138 Million) Series A For Antibody Programs in Neurodegenerative Diseases

Nov 13, 2023 - AMSTERDAM--(BUSINESS WIRE)--VectorY Therapeutics, a biotech company developing innovative vectorized antibody therapies for the treatment of neurodegenerative diseases, today announced the close of a €129 million ($138 million) Series A financing to advance its vectorized antibody programs in neurodegenerative diseases. The round was co-led by EQT Life Sciences and the Forbion Growth Opportunities Fund.

New and existing investors also participated in the financing, including MRL Ventures Fund, a corporate venture arm of Merck & Co., Inc., Rahway, NJ USA, Insight Partners, ALS Investment Fund, Forbion Ventures, BioGeneration Ventures (BGV) and another known investor.

VectorY will use the proceeds to support the clinical development of VTx-002, its lead vectorized antibody program targeting TDP-43 for the treatment of ALS. The Company will also accelerate the development of its vectorized antibody platform and additional pipeline programs targeting proteinopathies causing other neurodegenerative diseases.

"The Series A financing, supported by such a strong syndicate of European and US investors, is an endorsement of our pioneering approach, world-class team and commitment to bring much-needed therapies to patients with neurodegenerative diseases. The investment will enable us to advance our lead program VTx-002, a potentially disease-modifying therapy for ALS, into clinical development. Our program is uniquely positioned to address TDP-43 pathology, which underlies the disease in the vast majority of ALS patients. The series A will also support advancement of additional pipeline programs targeting proteinopathies in neurodegenerative diseases demonstrating the broad potential of our platform."

Sander Van Deventer
Chief Executive Officer
VectorY

Source: https://www.businesswire.com/news/home/20231113119625/en/VectorY-Raises-%E2%82%AC129-Million-138-Million-Series-A-Financing-to-Advance-Vectorized-Antibody-Programs-in-Neurodegenerative-Diseases

MBrace Therapeutics Raises $85 Million Financing for ADC Portfolio

Nov 14, 2023 – San Diego--MBrace™ Therapeutics, Inc. ("MBrace"), a privately-held biopharmaceutical company devoted to improving the lives of cancer patients through the development of antibody-drug conjugates (ADCs) against novel oncology targets, announced the completion of an $85 million Series B financing, bringing the company's total raised to $110 million. Funds will be used to support clinical development programs, including a first-in-human clinical trial of lead investigational ADC, MBRC-101.

TPG led the round, investing in the company through its dedicated life sciences fund, TPG Life Sciences Innovations (TPG LSI), and its multi-sector impact strategy, The Rise Fund. The round also included new investors Avidity Partners and Cowen Healthcare Investments, as well as existing Series A investors, Venrock and Alta Partners.

MBRC-101 targets the EphA5 receptor tyrosine kinase, which is present in multiple cancers including, but not limited to, breast, non-small cell lung (NSCLC), colorectal, gastric, and pancreatic cancers. The MBrace team will present preclinical data for MBRC-101 at the San Antonio Breast Cancer Symposium on December 7, 2023.

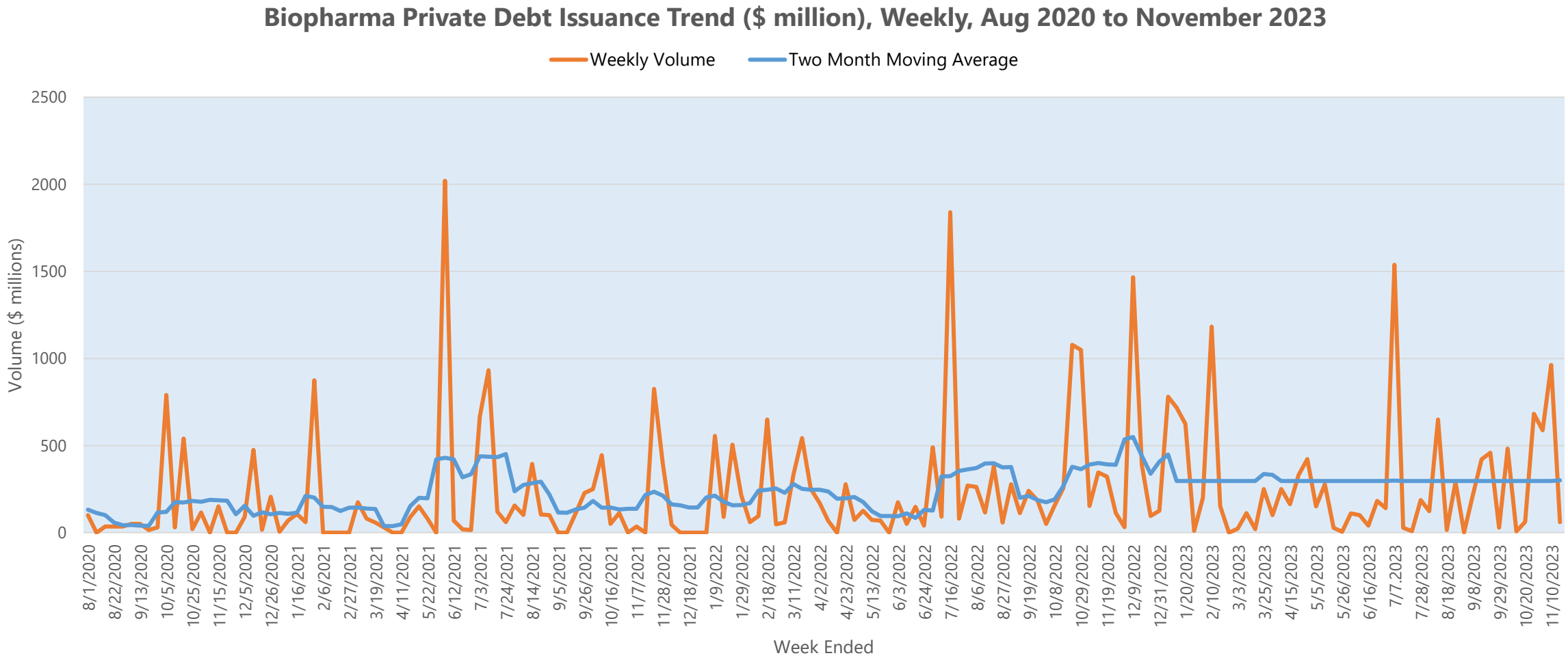
"This investor syndicate shares our confidence in the potential of our novel ADC therapeutics pipeline to meaningfully impact the treatment of people with difficult-to-treat cancers. This additional capital will enable us to advance our clinical programs, including entering Phase 1 study with MBRC-101 before end of year and progressing our differentiated approach to the clinical development of our additional ADC pipeline candidates. We are well poised to make significant progress in the near-term and continue on a positive growth trajectory."

Isan Chen
Chief Executive Officer
Mbrace Therapeutics

Source: https://www.businesswire.com/news/home/20231114082157/en/MBrace-Therapeutics-Raises-85-Million-Series-B-Financing-to-Advance-Oncology-Pipeline-of-Innovative-Antibody-Drug-Conjugate-Candidates

Weekly Global Biopharma Private Debt Placements

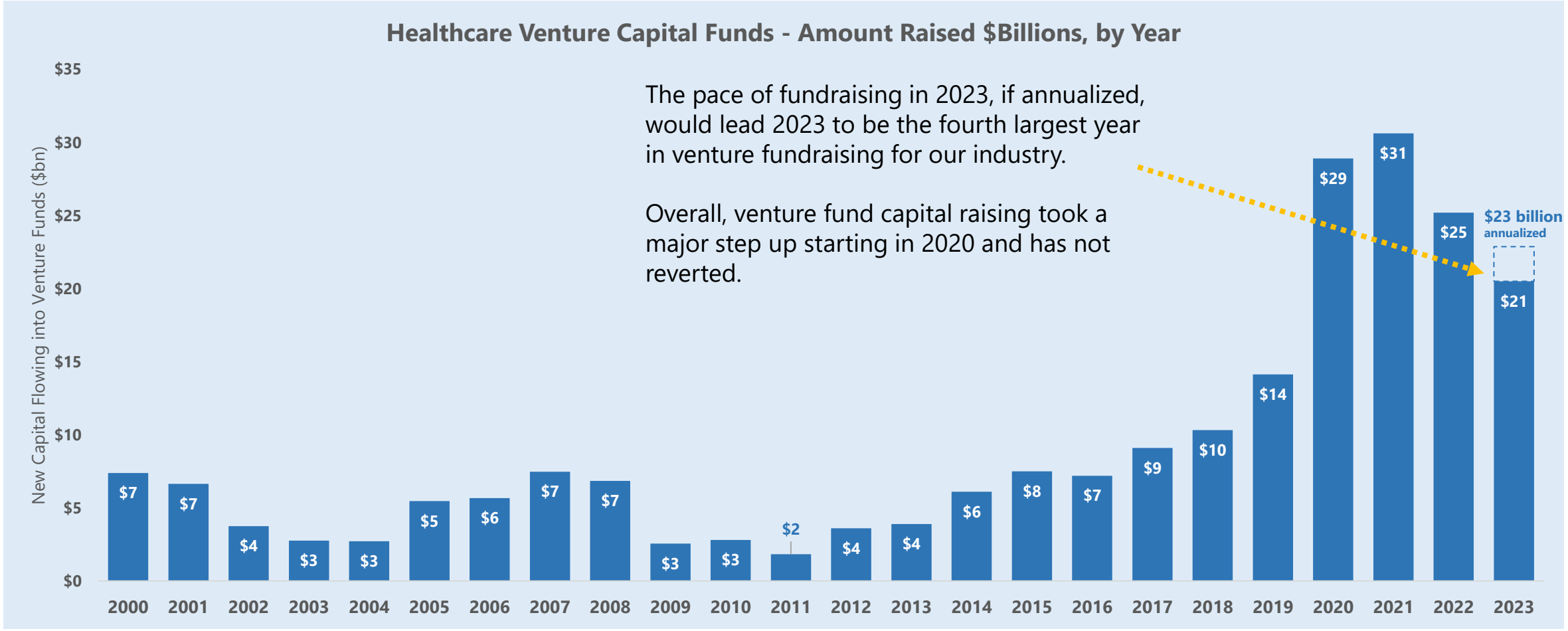
We saw four deals in the private debt market last week with $60 million raised. The largest deal was Acumen's placement of $50mm in venture debt with K2.



Source: Data from CapitalIQ, Crunchbase.

New Capital Flows Into Life Sciences Venture Funds Running at a $23 Billion Rate

There has been more venture money raised in our sector in the last five years than the prior nineteen years combined. This is a *huge* positive. We like to refer to this as the "wave of private capital".



Source: Stifel internal database

Gilde Healthcare Closes New Venture & Growth Fund at €740 Million

Nov 15, 2023: Gilde Healthcare today announces the final close of its Gilde Healthcare Venture&Growth VI fund with €740 million in commitments. Fund VI reached the hard cap following a first close at €600 million in April this year. The new fund focuses on fast growing companies developing solutions for better care at lower cost. Gilde Healthcare invests in companies in Europe and North America active in digital healthcare, medical technology (MedTech) and therapeutics. Gilde Healthcare Venture&Growth VI is an Article 9 Fund under the Sustainable Finance Disclosure Regulation (SFDR).

The fund is backed by a balanced mix of international investors, including healthcare corporates, (Dutch) pension funds, banks, insurers, fund-of-funds, sovereign wealth funds, endowments, family offices, entrepreneurs and the Gilde team.

The healthcare expenditure in the Western World continues to grow, already exceeding 20% of GDP in the United States. The society at large is in need of affordable solutions to counter this growth. Gilde Healthcare's mission to invest in better care at lower cost, is supported by a dedicated Impact Council, chaired by the former executive director of the European Medicines Agency (EMA).

The new fund will invest €10-70 million per new portfolio company. Together with the previous Venture&Growth fund (closed in 2020) and Gilde Healthcare Private Equity IV (closed in 2022), Gilde Healthcare has raised €1.7 billion in capital over the last three years.

"The strong interest from institutional investors driven to make a substantial impact, is a clear endorsement of our mission: investing in solutions to improve the quality of patient care while keeping it affordable. Our broad strategy, covering digital health, MedTech and therapeutics, results in a holistic approach allowing us to select the most optimal and cost effective solution for the individual patient. With a team of sector experts, we help companies to further scale medical innovations and to make them accessible globally."

Pieter van der Meer
Managing Partner
Gilde Healthcare

Source: https://gildehealthcare.com/news/general/gilde-healthcare-closes-new-venturegrowth-fund-at-e740-million-hard-cap/

Early OpenAI Investor Khosla Ventures Closes In on $3 Billion for Venture Funds

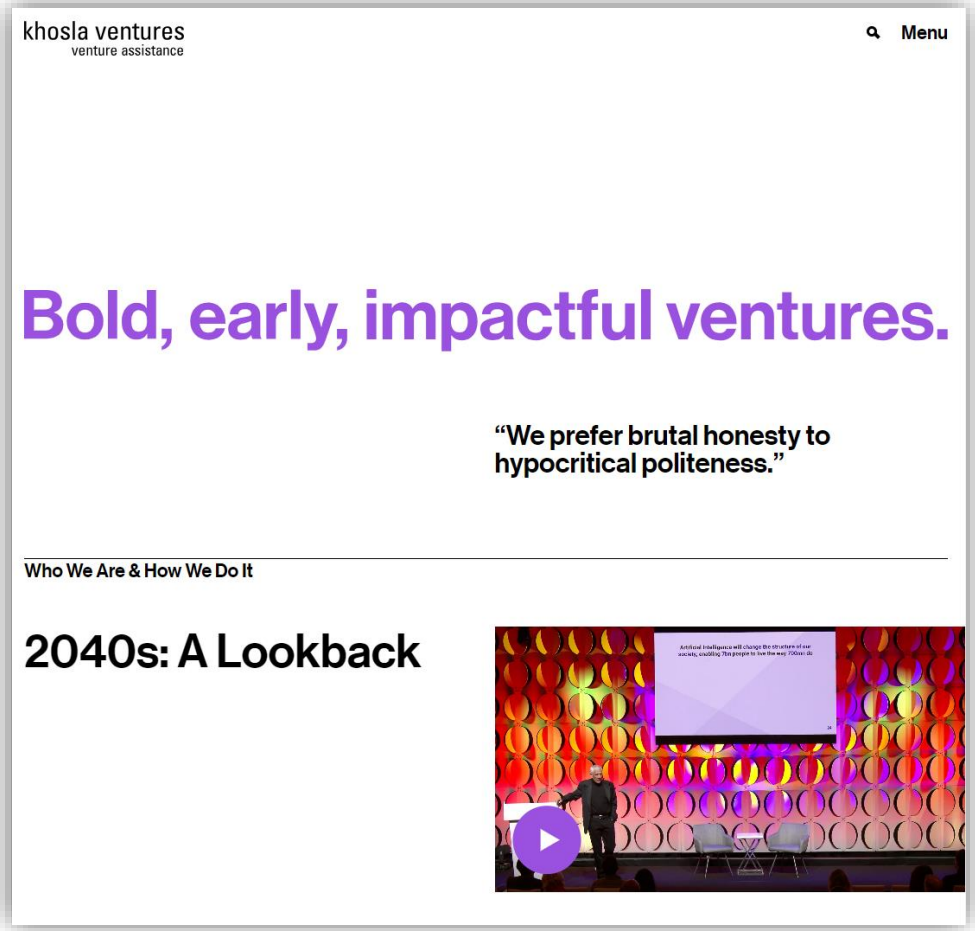
Berber Jin, *Wall Street Journal*, Nov 14, 2023 (excerpt)

Khosla Ventures is in the final stages of raising $3 billion for its latest set of venture funds, showing how some Silicon Valley investors remain bullish even as startups continue to stare down slower growth and lower valuations.

The fundraise will be one of the largest completed by a venture firm this year and one of the few to grow in size. Khosla Ventures, the first outside investor in ChatGPT creator OpenAI, last raised $1.85 billion three years ago.

The firm said it would focus on backing startups in research-intensive sectors such as nuclear fusion and humanoid robots. One investment area will be artificial intelligence, which has been an area of recent excitement in Silicon Valley even though many of the benefits have so far flowed to the tech giants.

Khosla Ventures sees the less competitive market as an opportunity to back startups aiming to bring technological changes to legacy industries such as **healthcare and transportation**. In 2019, the firm invested $50 million in OpenAI. That investment was more than double the largest first check Khosla Ventures had ever written for a startup.



Source: https://www.wsj.com/tech/khosla-ventures-closes-in-on-3-billion-for-venture-funds-defying-startup-slump-84f5a3fc

Industry News

View of Tokyo from the Imperial Palace Grounds

Welcome to the Brave New World of CRISPR Gene Editing

Greg Slabodkin, *Biospace*, November 17, 2023 (excerpt)

This past June marks the 11th anniversary of the development of CRISPR as a genome-editing tool, which earned Jennifer Doudna and Emmanuelle Charpentier the 2020 Nobel Prize in Chemistry. CRISPR-Cas9 technology was revealed to the world in the journal Science more than a decade ago, and it has translated into a gene editing revolution with big discoveries in a relatively short amount of time.

In a world first, the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) on Thursday approved CRISPR/Cas9 gene-edited therapy exagamglogene autotemcel (exa-cel)—developed by Vertex Pharmaceuticals and CRISPR Therapeutics, and now to carry the brand name Casgevy—as a potential cure for sickle cell disease (SCD) and transfusion-dependent beta thalassemia (TDT).

While the FDA is still reviewing exa-cel for the two blood disorders—with a PDUFA date of Dec. 8, 2023, for SCD and March 30, 2024, for TDT—there's every reason to believe the U.S. regulator will follow the lead of its British regulatory counterparts. And it's just the tip of the iceberg, as bluebird bio, Iovance and Rocket Pharmaceuticals wait patiently in the wings.

Currently, there are more than 50 in-human clinical trials of both in vivo and ex vivo gene editing technologies in the early stages and about 40 of them are CRISPR-based, according to David Liu, a molecular biologist at the Broad Institute and Harvard professor.

Source: https://www.biospace.com/article/welcome-to-the-brave-new-world-of-crispr-gene-editing/

First Trial of 'Base Editing' in Humans Lowers Cholesterol — but Raises Safety Concerns

Miryam Naddaf, *Nature*, November 13, 2023 (excerpt)

The first trial in humans of the precise gene-editing technique known as base editing has shown promising results for keeping cholesterol levels in check.

The approach involves an injection of a treatment called VERVE-101, which permanently deactivates a gene that is active in the liver called PCSK9. That gene controls the level of low-density lipoprotein (LDL), or 'bad' cholesterol — a key contributor to heart disease.

Verve Therapeutics, the biotechnology firm in Boston, Massachusetts, behind the treatment, reported that a one-time injection of VERVE-101 reduced the amount of LDL in the blood by up to 55% in trial participants, who had a condition that causes lifelong high LDL.

"It's a tremendous scientific milestone because it's the first time that they've been able to show that a single base pair of DNA editing, using CRISPR technology in humans, has had a clinical effect," says Ritu Thamman, a cardiologist at the University of Pittsburgh in Pennsylvania. "From the clinical point of view, it has the potential to open a new way of treating coronary artery disease" that could involve people receiving a 'one and done' treatment rather than taking daily pills.

But the findings have also drawn criticism. Two serious adverse events in the trial, including a death, have raised safety concerns, and Verve's share price plummeted by nearly 40% following the results' release.

Verve reported the interim results of a phase Ib trial, conducted in the United Kingdom and New Zealand, at a meeting of the American Heart Association in Philadelphia on 12 November. It will continue its trial next year in the United States, after receiving approval last month from the US Food and Drug Administration to enrol participants there.

Source: https://www.nature.com/articles/d41586-023-03543-z

Biden Taps Vanderbilt Physician-scientist to Head NCI

Kimryn Rathmell to become second director of the National Cancer Institute in just over 1 year

Science (Nov 17, 2023): It took nearly 2 years for President Joe Biden to find and the Senate to approve the new director of the U.S. National Institutes of Health (NIH), Monica Bertagnolli, who took her post last week. But Biden has moved to fill the newly vacant top job at NIH's largest institute, the National Cancer Institute (NCI), in a tiny fraction of that time.

Today, Biden announced that Vanderbilt University Medical Center physician-scientist Kimryn Rathmell will be NCI's 17th director. Rathmell will replace Bertagnolli, who served just over 1 year in the position before becoming NIH director. When Rathmell takes her position in December, she will be only the second woman to lead the $7.3 billion institute in its 86-year history.

In a statement announcing Rathmell's nomination, Biden called her a "talented and visionary leader" who "embodies the promise of the Biden Cancer Moonshot," his effort to cut the U.S. cancer death rate by 50% by 2047. "I look forward to working with her to help prevent, detect, and treat cancer to make sure Americans are living longer, healthier lives." In a separate statement, Bertagnolli described Rathmell as "an ideal candidate to lead NIH's efforts to end cancer as we know it."

Kimryn Rathmell, Incoming Head of NCI

Source: https://www.science.org/content/article/biden-taps-vanderbilt-physician-scientist-head-nci

Quest For Alzheimer's Cure: Big Biotech Breakthroughs, But The Race Is Just Beginning

Allison Gatlin, *Investor's Business Daily*, November 17, 2023 (excerpt)

The hunt for Alzheimer's treatments marked key victories this year, with breakthroughs from Biogen (BIIB), Eisai (ESAIY) and Eli Lilly (LLY). But investors in biotech stocks know the race for a cure for the memory-robbing disease is just getting started.

Now, experts say the floodgates could open up. The science behind the groundbreaking drugs is pointing a way forward. And the medical advances are expected to boost funding for Alzheimer's treatment research — and lift the stocks of companies working on a cure for the disease that affects more than 6 million Americans.

"I think it's an incredibly exciting time," **Prothena** (PRTA) Chief Executive Gene Kinney told Investor's Business Daily. "I do believe these advances in medicine will help move the field forward."

Furthermore, Leqembi and donanemab are far from ideal treatments. Both require semiregular infusions and MRI scans to find amyloid in the brain. They also carry the risk of brain swelling that's often asymptomatic, but can be fatal. Patients would prefer treatments in the form of shots or pills, Aaron Mitchell, a principal with consulting and technology firm ZS, said. Prothena's Kinney noted that even though Biogen and Eisai were first to market it doesn't mean they will ultimately be dominant. Prothena's bid to become a key player in the market hinges on its Alzheimer's drug's ability to block, not just amyloid, but also tau, another protein whose buildup in the brain is associated with the disease. The company is also working on several earlier-stage potential Alzheimer's treatments.

Smaller biotech companies have also joined the fray.

Acumen Pharmaceuticals (ABOS) is working on an Alzheimer's treatment that selectively binds to specific molecules of beta amyloid. In recent tests, patients experienced a 25% reduction in beta amyloid plaques over six to 12 weeks. That compares well to about 20% for Leqembi at the same time, analysts with Leerink Partners said in a recent report.

Another small biotech stock, **Vaxxinity** (VAXX) is working on a vaccine that would block toxic forms of amyloid beta. Vaxxinity Chief Executive Mei Mei Hu noted two forms of amyloid-related imaging abnormalities. The more serious form is known as ARIA-E, while ARIA-H "happens naturally and sporadically in older people," she told IBD. Vaxxinity reported promising results in a midstage test: its drug showed no instances of ARIA-E and "limited cases of asymptomatic ARIA-H."

Source: https://www.investors.com/news/technology/biotech-stocks-the-war-in-alzheimers-treatment-is-just-beginning-why-there-is-still-hope/

New Approaches Show Promise in Helping People With Low-Back Pain

Laura Landro, *Wall Street Journal*, November 14, 2023 (excerpt)

Millions of adults struggle for years with chronic low-back pain—a disabling ailment that has no easy fix. Common causes include injury, arthritis and degenerative changes in the spine. It tends to start at midlife with the natural wear and tear of aging. But often there is no clearly identifiable physical cause, leaving patients to veer from one ineffective treatment to another—including highly addictive prescription opioids.

Now, researchers are working on personalized treatment plans that can address physical, emotional and psychological traits in individual patients that influence the pain they are experiencing. Physical therapy, exercise, diet and lifestyle choices often play a role. Some research is also looking at ways to retrain the brain to think differently about pain.

At that point he was referred to the UPMC spine-health program, where he says the spine-specific, personalized physical therapy helped him begin feeling better after three weeks, strengthening his abdominal muscles and providing him with exercises to do at home. A spine-health psychologist helped him better manage his mental outlook and adapt his lifestyle to his situation, he says. A dietitian recommended an anti-inflammatory diet with more fresh fruits and whole grains, and a medical masseuse helped loosen up muscles that had been problematic, improving his gait enough to enable hiking on rugged trails with the use of walking sticks. He started Pilates classes to build core strength and improve balance.

Rossitto says the program has helped him take greater control of managing his pain and reduce stress and anxiety. He no longer uses opioids or other pain medications, and he sticks to his home regimen of exercises and stretches. From an average day with a pain level of 7 or 8 out of 10 in 2017, "'I am now at about a 5, and on good days a 4."

Source: https://www.wsj.com/health/healthcare/lower-back-pain-non-surgical-treatment-a9df097f

PureTech's Oral Allopregnanolone Achieved Endpoint in a Phase 2a Acute Anxiety Trial

Nov. 14, 2023 News Release – PureTech, a clinical-stage biotherapeutics company dedicated to changing the lives of patients with devastating diseases, today announced topline results from its Phase 2a, randomized, placebo-controlled, proof-of-concept trial of LYT-300 (oral allopregnanolone). The trial was designed to evaluate the salivary cortisol response in the Trier Social Stress Test (TSST), a validated clinical model of anxiety in healthy volunteers.

Oral administration of LYT-300 achieved the trial's primary endpoint of a statistically significant reduction versus placebo in the increase from baseline to peak levels of the stress hormone salivary cortisol (p=0.0001). The LYT-300 treatment effect size versus placebo was 0.72, as measured by Cohen's d, which is one of the most common ways to measure effect size. LYT-300 showed a similar effect size to previously observed results for alprazolam, a benzodiazepine drug indicated for treatment of anxiety disorders, when assessed following the TSST procedure2. An increase in cortisol levels after the TSST is a physiological response and an objective biomarker of acute stress. Eighty healthy volunteers were randomized and treated with either LYT-300 or placebo in a 1:1 ratio. LYT-300 was well tolerated, with all treatment-related adverse events transient, mild or moderate and consistent with the known pharmacology profile of allopregnanolone. Additional data from the study will be presented in a scientific forum.

"These data validate that LYT-300 has potential to make a difference for people living with anxiety, where there's been a dearth of innovation and existing treatments have drawbacks," said Daphne Zohar, Founder and Chief Executive Officer of PureTech Health. "The successful outcome of this trial builds on our strategy of identifying drugs with proven clinical efficacy but with historical limitations that have held back their therapeutic use, and then applying an innovative solution to enhance their potential for patients. In the CNS arena, we previously applied this strategy to invent KarXT for the treatment of schizophrenia. Building on this approach, we now have seven wholly owned CNS programs powered by our GlyphTM platform, which is designed to enable the oral bioavailability of drugs with high first-pass metabolism and resolve hepatotoxicity."

Source: https://news.puretechhealth.com/news-releases/news-release-details/puretechs-lyt-300-oral-allopregnanolone-achieved-primary

Some Challenging News Stories Last Week

Fiduciary breach claims

Nov. 17, 2023 Law360 – Unjust enrichment and fiduciary breach claims against six directors or officers of biotech venture Northwest Biotherapeutics moved toward trial late Friday after a Delaware vice chancellor refused to dismiss claims that they failed to disclose real motives for dealing themselves more than $40 million in stock awards.

Clinical Data Fraud Allegations

November 15, 2023 – Biospace: Phase II data supporting ZZ Biotech's investigational stroke therapy 3K3A-APC might have been doctored to make the candidate appear safer and more effective than it actually is, according to an investigative report by the journal *Science*, citing a small group of whistleblowers. The whistleblowers produced a 113-page dossier—which has already been submitted to the NIH.

Bribery and FCPA Issue

Nov. 17, 2023 FCPA Blog. Lifecore Biomedical, Inc., formerly known as Landec Corporation, received a declination with disgorgement Friday from the DOJ for FCPA violations in Mexico.

Unjust Enrichment

Nov 10, 2023, FierceBiotech. The Nymox Pharmaceutical versus AscellaHealth drama has heightened, with the battle heading to court as Nymox seeks $250 million in damages. The biotech is following up on a promise made this summer, when it pledged to hold the pharmaceutical solutions provider responsible for damages arising from its connection to former Nymox leaders that damaged the relationship between the biotech and its shareholders. The new suit was filed in California Superior Court, Orange County, to protect Nymox's shareholders' interests, according to a Nov. 9 company release. Following an FDA rejection, AscellaHealth exchanged business information with Nymox under a nondisclosure agreement and extended a partnership offer. At the time, Nymox's Chief Financial Officer Christopher Riley launched "The Committee to Restore Nymox Shareholder Value," and pushed for the pact with Pennsylvania-based AscellaHealth, with whom it was later discovered that Riley had an ongoing business association with.

Source: https://www.law360.com/articles/1764351/chancery-refuses-toss-of-biotech-firm-share-award-suit, https://fcpablog.com/2023/11/17/biotech-company-receives-declination-with-disgorgement-for-mexico-bribes/, https://www.biospace.com/article/zz-biotech-hit-with-data-manipulation-allegations-regarding-stroke-trial/, https://www.fiercebiotech.com/biotech/nymox-drama-heightens-biotech-sues-ascellahealth-250m-damages

Eli Lilly Plans New €2 Billion German Plant

Rene Wagner, Klaus Lauer and Andreas Rinke, *Reuters*, Nov 16, 2023 (excerpt)

BERLIN, Nov 16 (Reuters) - U.S. pharmaceuticals company Eli Lilly (LLY.N) plans to build a production plant in western Germany, sources close to the matter told Reuters, with one putting the investment at 2 billion euros ($2.17 billion).

The new site, Lilly's first major production complex in Germany, comes as drugmakers are growing increasingly sensitive to political pressure to manufacture critical healthcare products closer to the markets they serve after the coronavirus pandemic exposed the vulnerability of global supply chains.

Two of the sources said that more than 1,000 jobs would be created, when including an expected boost to sub-contractors and suppliers in the region.

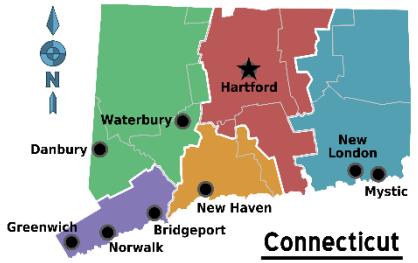
The company declined to comment on the plans but news conferences have been scheduled in the town of Alzey, where sources say the plant will be built, and Berlin on Friday.

The project will be fully funded by the medicines giant, which has seen surging demand for its diabetes drug Mounjaro, people familiar with the matter had told Reuters on Wednesday.

One of the sources said that the new site would make diabetes drugs with the potential use to treat obesity. No further details were available on what the plant would produce.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/eli-lilly-plans-new-2-bln-euro-german-plant-source-2023-11-16/

Connecticut Has a Behavioral Plan for Dealing with Weight Loss Drug Cost



Advisory Board, Nov 17, 2023

As states and employers grapple with the high costs of these weight-loss drugs, a new program being tested in Connecticut may provide a roadmap to providing coverage for these drugs while mitigating costs.

In July, Connecticut introduced a new clinical lifestyle management program called Flyte for state health plan members who want to take drugs such as Ozempic or Wegovy for weight loss. The program offers online tools for weight management, and participants can meet with providers to receive personalized care plans.

Providers who are part of Flyte can prescribe GLP-1 drugs, which the state health plan would then cover, or recommend a different course of treatment for patients. "I never considered getting rid of the drugs, but I also knew that the status quo was not going to work and we had to look at other options," said Connecticut Comptroller Sean Scanlon, who runs the state health plan, which covers 265,000 employees. This year, before the introduction of Flyte, the health plan was on course to spend $30 million on weight loss drugs.

So far, the Flyte program, which is administered through a company called Intellihealth, is showing early signs of success. As of Nov. 3, around 1,501 members of the state health plan have signed up for the program. Although doctors have written prescriptions for GLP-1 prescriptions for around 80% of these patients, the number of new prescriptions is plateauing. Previously, the plan had seen a 50% yearly growth in new prescriptions for these drugs.

According to Intellihealth CEO Sloan Saunders, the company uses a comprehensive approach to obesity where providers consider different treatment plans, including lower-cost therapies, before prescribing expensive weight-loss drugs.

"Just prescribing someone Wegovy and sending them on their way really doesn't get great outcomes," Saunders said.

Connecticut currently pays around $110 a month for each participant in the program, and based on the current number of patients participating, the annual cost would be roughly $2 million. The state plans to evaluate results over a 10-month period and will collect feedback from employees before it decides whether to commit to a more long-term contract with Intellihealth.

Source: https://www.advisory.com/daily-briefing/2023/11/17/connecticut-weight-loss

Does a Population Program for Behavioral PreDiabetes Control Work? UK Experiment

Quasi-experimental evaluation of a nationwide diabetes prevention programme

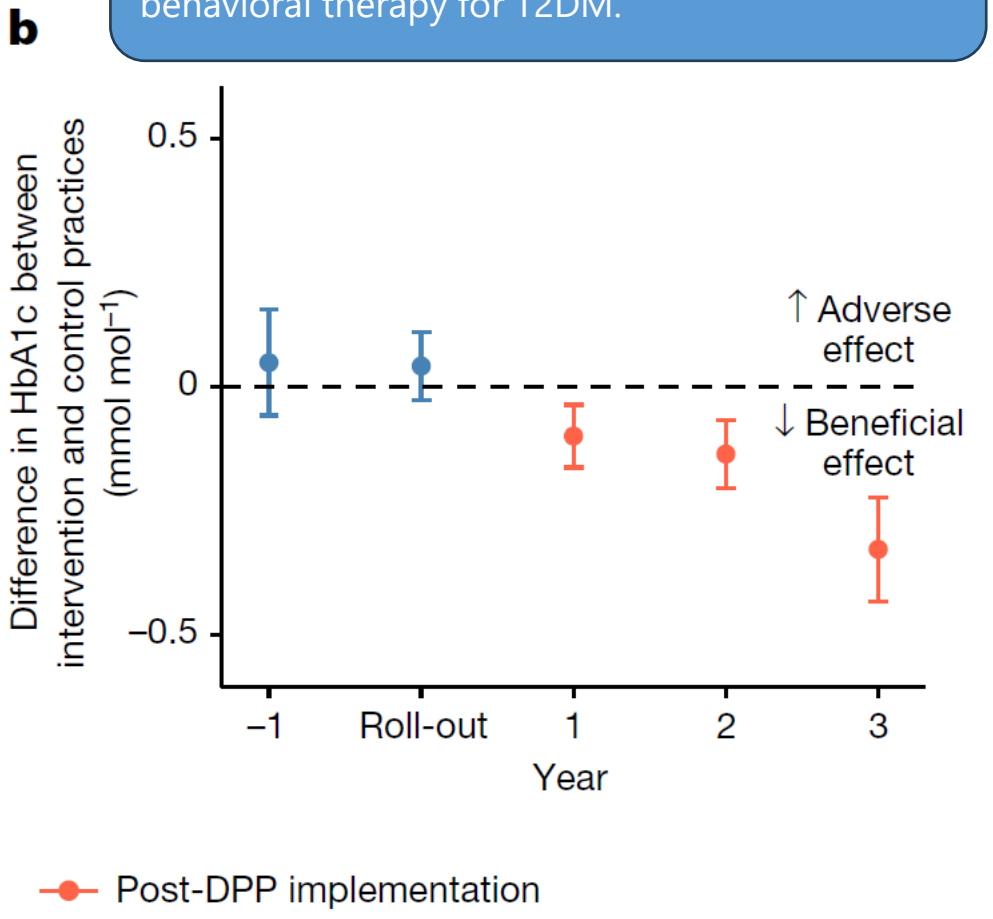
Nature

https://doi.org/10.1038/s41586-023-06756-4
Received: 19 May 2022
Accepted: 17 October 2023
Published online: 15 November 2023

Julia M. Lemp[1,2], Christian Bommer[1,3], Min Xie[1,2], Felix Michalik[1,2], Anant Jani[1,4], Justine I. Davies[5,6,7], Till Bärnighausen[1,8,9], Sebastian Vollmer[3] & Pascal Geldsetzer[2,10,11]

Diabetes is a leading cause of morbidity, mortality and cost of illness[1,2]. Health behaviours, particularly those related to nutrition and physical activity, play a key role in the development of type 2 diabetes mellitus. Whereas behaviour change programmes (also known as lifestyle interventions or similar) have been found efficacious in controlled clinical trials, there remains controversy about whether targeting health behaviours at the individual level is an effective preventive strategy for type 2 diabetes mellitus and doubt among clinicians that lifestyle advice and counselling provided in the routine health system can achieve improvements in health. Here we show that being referred to the largest behaviour change programme for prediabetes globally (the English Diabetes Prevention Programme) is effective in improving key cardiovascular risk factors, including glycated haemoglobin (HbA1c), excess body weight and serum lipid levels. We do so by using a regression discontinuity design, which uses the eligibility threshold in HbA1c for referral to the behaviour change programme, in electronic health data from about one-fifth of all primary care practices in England. We confirm our main finding, the improvement of HbA1c, using two other quasi-experimental approaches: difference-in-differences analysis exploiting the phased roll-out of the programme and instrumental variable estimation exploiting regional variation in programme coverage. This analysis provides causal, rather than associational, evidence that lifestyle advice and counselling implemented at scale in a national health system can achieve important health improvements.

The effect size seen in this massive experiment in the NHS was quite small. Don't bet big on behavioral therapy for T2DM.

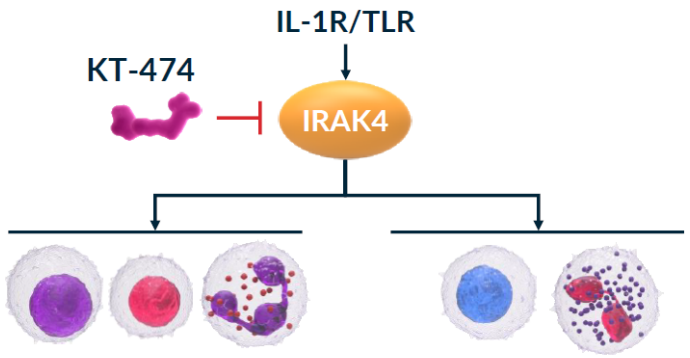


Source: https://www.nature.com/articles/s41586-023-06756-4

Sanofi / Kymera IRAK4 Degrader Highlighted Last Week

IRAK4 Degrader Best-in-Class Potential in Immune-inflammation

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Lupus
- IBD
- Gout
- Psoriasis

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

~$120B Combined global drug sales

Indication	2022 Prevalence[1] (US/EU5/JP)	2022 Global Sales[2]
AD	98 M	$8.6 B
HS	785 K	$1.0 B[1]
RA	6.4 M	$27.9 B
SLE	550 K	$1.8 B
IBD	3.1 M	$23.6 B
Gout	20.3 M	$1.1 M
Psoriasis	15.8 M	$24.6 B
Asthma	86.8 M	$17.7 B
COPD	61.9 M	$9.6 B
CRSwNP	20.4 M[3]	$2.6 B[4]

Limitations of Current Therapies

- **Anti-Cytokine/Cytokine Receptor Antibodies**
  - Target only 1-2 cytokines
  - Require injection
- **Small Molecule Inhibitors**
  - Limited pathway blockade (IRAK4 SMI)
  - Safety issues (JAK family)

Source: 1. GlobalData; 2. Evaluate Pharma;.3. Ahn. JAMA Otolaryngol Head Neck Surg. 2016; 4. Dash. Allied Market Research 2021

Data Out Last Week in *Nature Medicine* Shows Impressive Results in both HS and AD

nature medicine

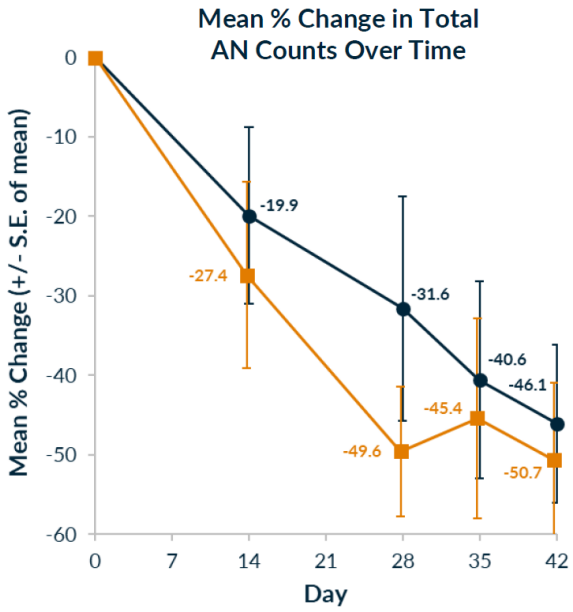
Article

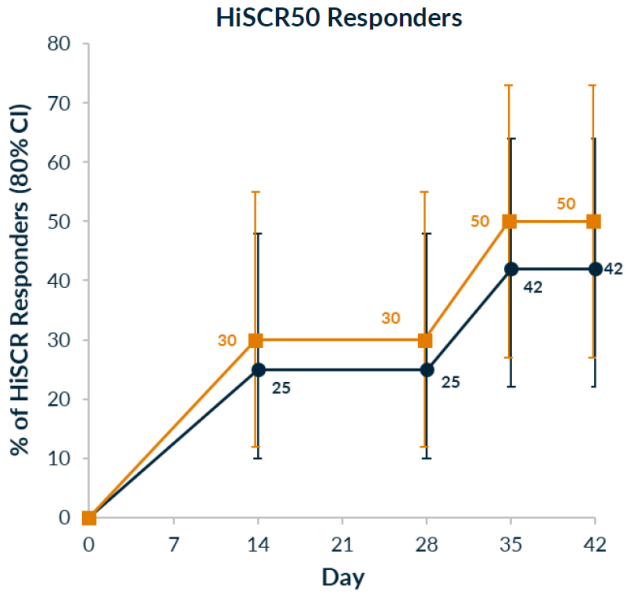
https://doi.org/10.1038/s41591-023-02635-7

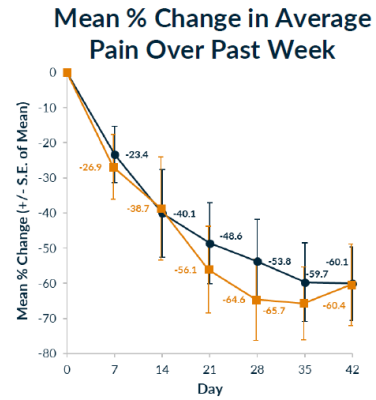
IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial

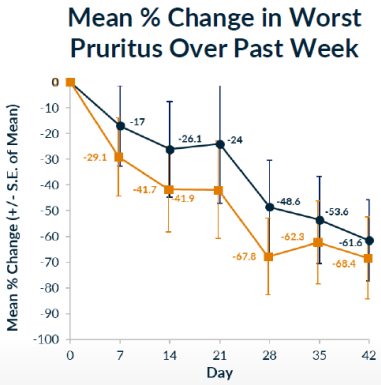
IRAK4 Patients

KT-474 HS: Significant Reductions in AN Counts Leading to HiSCR Responses and Significant Reductions in Pain and Pruritis









All HS Patients (N=12)*
Moderate to Severe (N=10)

*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

Source: https://www.nature.com/articles/s41591-023-02635-7

CAR-T Cell Therapy Leads to Long-Term Remission in Lupus While Maintaining Vaccine Response

American College of Rheumatology, Nov. 7, 2023 News Release -- New research at ACR Convergence 2023, the American College of Rheumatology's annual meeting, demonstrates that CAR-T cell therapy could lead to sustained suppression of autoantibodies in treatment-resistant lupus while maintaining a robust response to vaccines (Abstract #0607).

The disease often requires life-long treatment with immunosuppressive or immunomodulatory drugs, and a considerable number of patients don't respond to them. One theoretical option for these patients is chimeric antigen receptor (CAR)-T cell therapy, which is successfully used to treat refractory blood cancers by destroying malignant cells.

"We were intrigued by the possibility that a deep B cells depletion exerted by CAR-T cells could lead to permanent eradication of the autoimmune disease," says Georg Schett, MD, a rheumatologist at the University Hospital Erlangen in Germany.

CAR-T cells are created by removing some of a patient's white blood cells, including immune system T cells, and genetically altering them in a lab to produce chimeric antigen receptors (CARs). The modifications allow the treated T cells to recognize and destroy antigens on the surface of target pathogenic cells after they are infused back into the patient.

Schett and his colleagues published the first-ever study of CAR-T therapy for lupus in 2022. The CAR-T cells were engineered to target CD19, a protein on the surface of the B cells that trigger lupus flares. At three months, all five patients in the study achieved drug-free remission, which was maintained up to a median eight months after the infusion.

The current follow-up study aimed to learn whether remission in CD19 CAR-T cell-treated patients could be sustained further and whether depleting B cells would blunt the effectiveness of vaccines, which work through B cells to drive antibody response.

Source: https://www.eurekalert.org/news-releases/1007311

Data from Dr. Schett's Presentation at ACR, Nov 14th

Short-Term Efficacy of CD19 CAR T cell therapy in autoimmune disease

Patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
DORIS Remission	+	+	+	+	+	+	+	+*	n/a	n/a	n/a	n/a	n/a	n/a	n/a
LLDAS	+	+	+	+	+	+	+	+*	n/a	n/a	n/a	n/a	n/a	n/a	n/a
SLEDAI	0	0	0	0	0	0	0	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ACR/EULAR Major improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+*	n/a	n/a	n/a	n/a
CK Normalization	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+*	n/a	n/a	n/a	n/a
EUSTAR AI Improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-3,6	-4.3	-4.3	#
mRSS Improvement	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-7	-9	-11	#
Glucocorticoid-free state	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+**
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+**

DORIS, Definition Of Remission In SLE; EUSTAR-AI, European Scleroderma Trials and Research Group Activity Index; IIM, idiopathic inflammatory myopathy; LLDAS, Lupus Low Disease Activity State ; mRSS, modified Rodnan skin score; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SSc, systemic sclerosis; * based on 3 months data**based on 2 months data; # short observation <3 months;

CAR-t delivering full remission in lupus in all patients tested.

Source: https://acrabstracts.org/abstract/efficacy-and-safety-of-car-t-cell-treatment-in-refractory-antisynthetase-syndrome-data-of-the-first-three-patients/

Safety and efficacy of gene replacement therapy for X-linked myotubular myopathy (ASPIRO): a multinational, open-label, dose-escalation trial

Perry B Shieh, Nancy L Kuntz, James J Dowling, Wolfgang Müller-Felber, Carsten G Bönnemann, Andreea M Seferian, Laurent Servais, Barbara K Smith, Francesco Muntoni, Astrid Blaschek, A Reghan Foley, Dimah N Saade, Sarah Neuhaus, Lindsay N Alfano, Alan H Beggs, Ana Buj-Bello, Martin K Childers, Tina Duong, Robert J Graham, Minal Jain, Julie Coats, Vicky MacBean, Emma S James, Jun Lee, Fulvio Mavilio, Weston Miller, Fatbardha Varfaj, Michael Murtagh, Cong Han, Mojtaba Noursalehi, Michael W Lawlor, Suyash Prasad, Salvador Rico

Summary

Background X-linked myotubular myopathy is a rare, life-threatening, congenital muscle disease observed mostly in males, which is caused by mutations in *MTM1*. No therapies are approved for this disease. We aimed to assess the safety and efficacy of resamirigene bilparvovec, which is an adeno-associated viral vector serotype 8 delivering human *MTM1*.

Methods ASPIRO is an open-label, dose-escalation trial at seven academic medical centres in Canada, France, Germany, and the USA. We included boys younger than 5 years with X-linked myotubular myopathy who required mechanical ventilator support. The trial was initially in two parts. Part 1 was planned as a safety and dose-escalation phase in which participants were randomly allocated (2:1) to either the first dose level ($1·3×10^{14}$ vector genomes [vg]/kg bodyweight) of resamirigene bilparvovec or delayed treatment, then, for later participants, to either a higher dose ($3·5×10^{14}$ vg/kg bodyweight) of resamirigene bilparvovec or delayed treatment. Part 2 was intended to confirm the dose selected in part 1. Resamirigene bilparvovec was administered as a single intravenous infusion. An untreated control group comprised boys who participated in a run-in study (INCEPTUS; NCT02704273) or those in the delayed treatment cohort who did not receive any dose. The primary efficacy outcome was the change from baseline to week 24 in hours of daily ventilator support. After three unexpected deaths, dosing at the higher dose was stopped and the two-part feature of the study design was eliminated. Because of changes to the study design during its implementation, analyses were done on an as-treated basis and are deemed exploratory. All treated and control participants were included in the safety analysis. The trial is registered with ClinicalTrials.gov, NCT03199469. Outcomes are reported as of Feb 28, 2022. ASPIRO is currently paused while deaths in dosed participants are investigated.

Findings Between Aug 3, 2017 and June 1, 2021, 30 participants were screened for eligibility, of whom 26 were enrolled; six were allocated to the lower dose, 13 to the higher dose, and seven to delayed treatment. Of the seven children whose treatment was delayed, four later received the higher dose (n=17 total in the higher dose cohort), one received the lower dose (n=7 total in the lower dose cohort), and two received no dose and joined the control group (n=14 total, including 12 children from INCEPTUS). Median age at dosing or enrolment was 12·1 months (IQR 10·0–30·9; range 9·5–49·7) in the lower dose cohort, 31·1 months (16·0–64·7; 6·8–72·7) in the higher dose cohort, and 18·7 months (10·1–31·5; 5·9–39·3) in the control cohort. Median follow-up was 46·1 months (IQR 41·0–49·5; range 2·1–54·7) for lower dose participants, 27·6 months (24·6–29·1; 3·4–41·0) for higher dose participants, and 28·3 months (9·7–46·9; 5·7–32·7) for control participants. At week 24, lower dose participants had an estimated 77·7 percentage point (95% CI 40·22 to 115·24) greater reduction in least squares mean hours per day of ventilator support from baseline versus controls (p=0·0002), and higher dose participants had a 22·8 percentage point (6·15 to 39·37) greater reduction from baseline versus controls (p=0·0077). One participant in the lower dose cohort and three in the higher dose cohort died; at the time of death, all children had cholestatic liver failure following gene therapy (immediate causes of death were sepsis; hepatopathy, severe immune dysfunction, and pseudomonal sepsis; gastrointestinal haemorrhage; and septic shock). Three individuals in the control group died (haemorrhage presumed related to hepatic peliosis; aspiration pneumonia; and cardiopulmonary failure).

Interpretation Most children with X-linked myotubular myopathy who received *MTM1* gene replacement therapy had important improvements in ventilator dependence and motor function, with more than half of dosed participants achieving ventilator independence and some attaining the ability to walk independently. Investigations into the risk for underlying hepatobiliary disease in X-linked myotubular myopathy, and the need for monitoring of liver function before gene replacement therapy, are ongoing.

Lancet Neurol 2023; 22: 1125–39

See Comment page 1089

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Lancet Neurology Paper Explains Four Deaths Seen in Astellas MTM1 Gene Therapy Trial

Biopharma Dive (Nov 16, 2023): A new paper published online in *The Lancet Neurology* Wednesday provides key new details on a gene therapy study that left four patients dead and posed broader questions about safety for the emerging field.

The article lays out data from the so-called Aspiro trial of Astellas Pharma's AT132, a therapy designed to treat X-linked myotubular myopathy, a rare neuromuscular condition that almost exclusively affects young boys. The disease leads to death within the first 18 months of life for about half of affected individuals, often robbing children of the ability to sit up, eat or breathe.

Now, researchers are suggesting a link to pre-existing liver function issues. All four patients who died in the treatment group had serious hepatobiliary issues, compared with five of the 20 surviving patients who received the therapy, Astellas said Wednesday. The propensity of some children with X-linked myotubular myopathy patients to have cholestatic liver disease was previously unknown, researchers said.

Source: https://www.biopharmadive.com/news/astellas-gene-therapy-xlmtm-lancet-paper-safety/700049/

Some Slides from Atlas Venture Year in Review 2023

Atlas Venture Year in Review

We confess to being complete junkies for the Atlas Venture "Year in Review" and watch the release each year with high interest.

This year was not an exception.

Bruce Booth of Atlas provided a review of the market that was intelligent, thoughtful, engaging and interesting.

We carry a few select slides here but really encourage to go and watch the review yourself on YouTube. The link is in the downloadable deck.

Some key slides in this section that caught our attention:

The detail on the decade of immunology and associated mechanisms
The amazing set of late-stage assets in development in biopharma today
A chart showing the risk of biopharma programs
The large backlog of later stage private companies waiting to go public
The importance of bolt-on M&A in bolstering the public markets
The parallels of today's market to that of 2003 and
The argument that the recovery from today's downturn will be different than that of 2003.

Source: https://www.youtube.com/watch?v=0DlgT32bFV4

I&I: DECADE OF IMMUNOLOGY CONTINUES

Big New Drugs & Data

Mechanism	Drug	Sponsor
TYK2	Sotyktu	Bristol Myers Squibb
	TAK-279	Takeda, nimbus THERAPEUTICS
FcRN	Vyvgart	argenx
	Rystiggo	ucb
	IMVT-1402	IMMUNOVANT
IL17	Sonelokimab	MoonLake
	DC-806	DICE, Lilly

Mechanism	Drug	Sponsor
IL23	JNJ-2113	Johnson&Johnson, Protagonist Therapeutics
TL1A	PRA023	Prometheus Biosciences, MERCK
	RVT-3101	Telavant, Pfizer, Roche
	TEV-48574	teva, sanofi
TSLP	Tezspire	AMGEN, AstraZeneca
IL4 / IL13	Dupixent	sanofi, REGENERON
	Lebrikizumab	Lilly

Other Mechanisms

- IRAK4
- STAT6
- STAT3
- MK2
- SIK
- IL31R / OSMR
- MRGPRX2

LATE STAGE ASSETS: DIVERSE & COMPELLING

MERCK — External

MK-0616

Oral PCSK9

— FOR —

Hypercholesterolemia

bridgebio — External

ACORAMIDIS

TTR stabilizer

— FOR —

ATTR-Cardiomyopathy

AMGEN

AMG-133

GLP1 agonist / GIPR antagonist

— FOR —

Obesity

Johnson&Johnson — External

JNJ2113

Oral IL23 antagonist

— FOR —

Psoriasis

VERTEX

VX-548

Nav1.8 inhibitor

— FOR —

Pain

MIRATI THERAPEUTICS

MRTX 1719

PRMT5 inhibitor

— FOR —

Solid Tumors

RISK: HIGH PROFILE FAILURES ARE PART OF THE BUSINESS

FDA — Sage Therapeutics
Zuranolone
– FOR –
Depression (MDD)

Data — FibroGen
Pamrevlumab
– FOR –
IPF

Safety — Apellis
Syfovre
– FOR –
Vasculitis

Data — Roche
Gantenerumab
– FOR –
Alzheimer's Disease

FDA — Intercept
OCA
– FOR –
NASH

Data — ACELYRIN
Izokibep
– FOR –
Hidradenitis Suppurativa

All — EQRx
Entire Business Model

Data — Benevolent AI
BEN-2293 (pan-TRKi)
– FOR –
Atopic Dermatitis

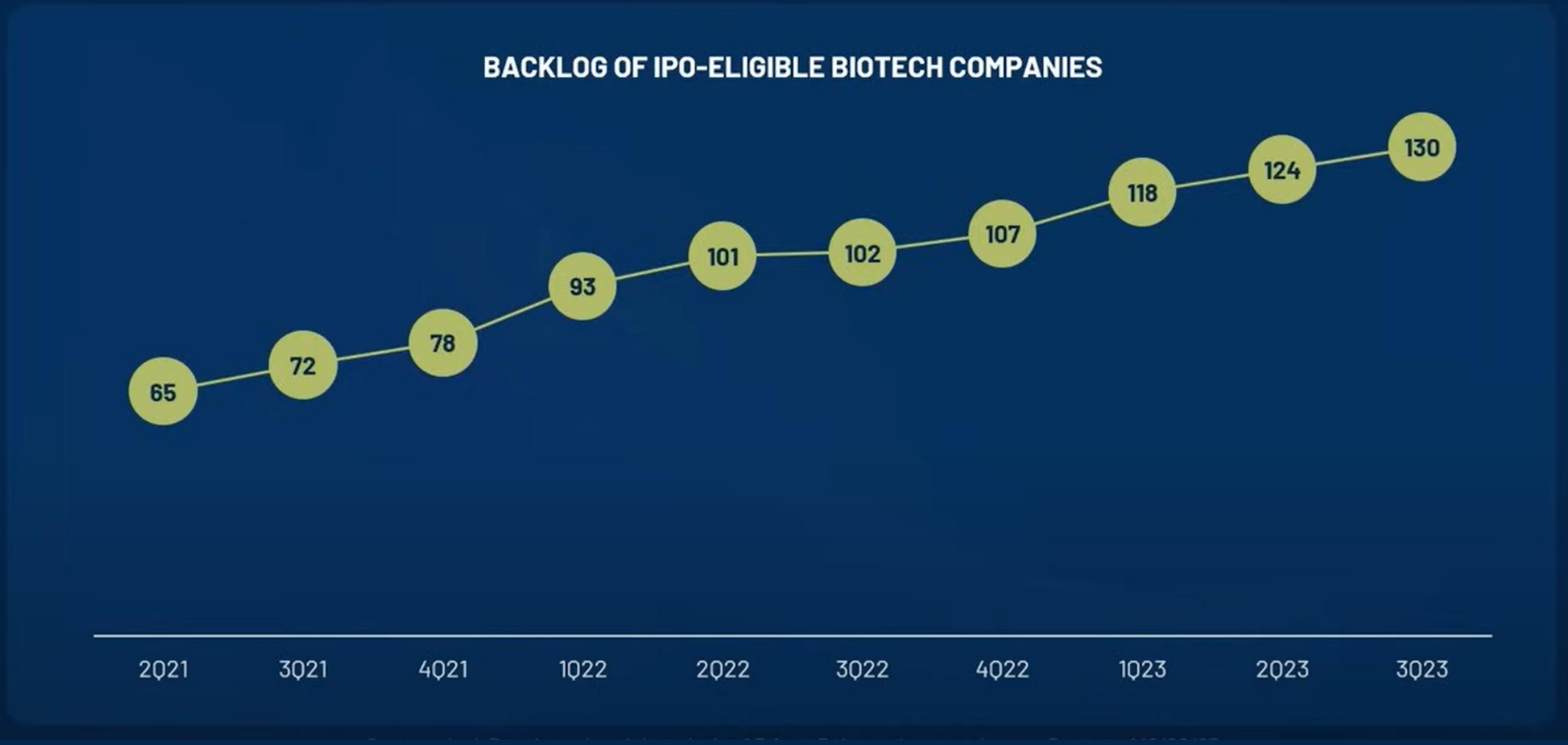
Source: Atlas analysis of company press releases

FTC: M&A AVOIDS GETTING KHAN-CELED?

AMGEN HORIZON

- Creating hesitation on part of buyers
- FTC risk very present in every deal dialogue
- Uncertainty is risk
- Impact on actual deals remains to be seen

LACK OF IPOs CREATES BACKLOG OF LATER STAGE PRIVATES



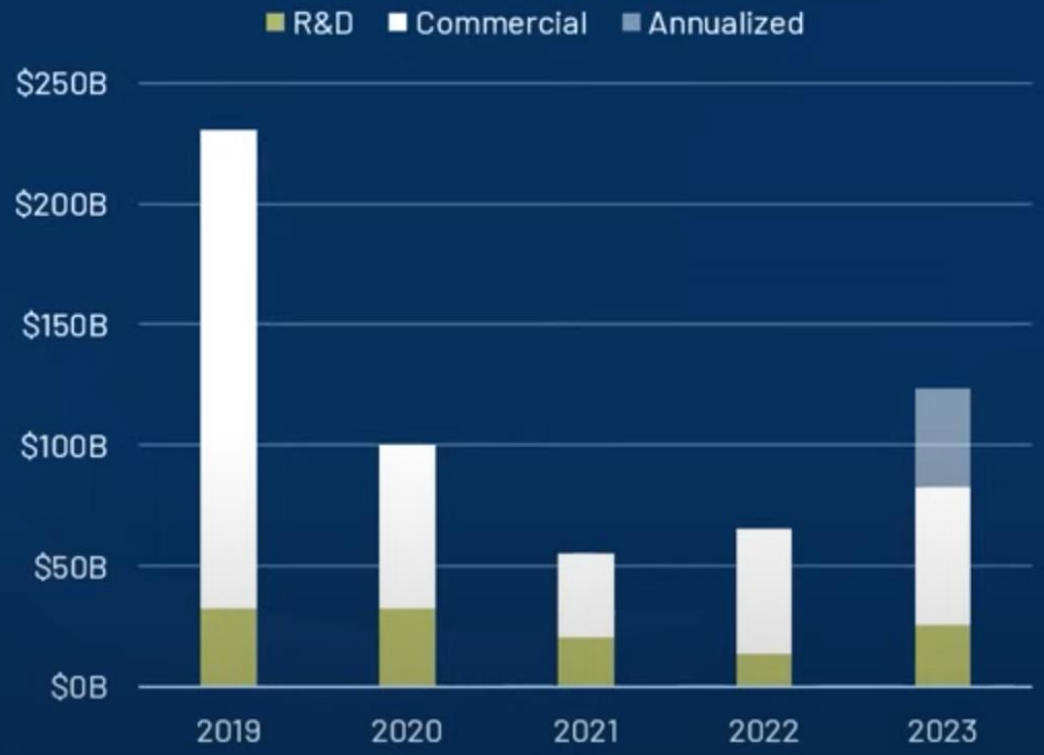
BOLT-ON M&A BY PHARMA UNDERPINNING THE MARKETS

TOP 9 PUBLIC M&A DEALS

TARGET	ACQUIRER	TOTAL DEAL VALUE
SeattleGenetics	Pfizer	$42.8B
Prometheus Biosciences	MERCK	$10.2B
REATA	Biogen	$7.2B
MIRATI THERAPEUTICS	Bristol Myers Squibb	$5.8B^
IVERIC BIO	astellas	$5.4B
CHINOOK THERAPEUTICS	NOVARTIS	$3.1B
proventionbio	sanofi	$2.7B
DICE Therapeutics	Lilly	$1.9B
Bellus HEALTH	GSK	$1.7B

PUBLIC M&A*

Total Deal Value



Notes: * Excluding SPACs and Reverse Mergers; ^ Includes CVR Source: Atlas analysis of BMO Capital Markets dataset

Data as of 8/31/23; Excludes deals <$50M in size and involving generics, biosimilars, reformulations, drug delivery, devices, diagnostics, manufacturing, etc. deals

SO WHERE ARE WE? ...WHAT HAPPENED LAST TIME (~2003)?

IPO MARKETS WERE BAD FOR THE REST OF THE DECADE

nature biotechnology

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Published: August 2009

Beyond the biotech IPO: a brave new world

Bruce L Booth

Nature Biotechnology **27**, 705–709 (2009) | Cite this article

906 Accesses | **21** Citations | **19** Altmetric | Metrics

After a decade of significant challenges, biotech's long-term sustainability depends on making fundamental changes to its traditional business model.

Source: Booth BL Nature Biotech (2009)

MANY VC FIRMS DISAPPEARED

MAJOR LIFE SCIENCE VENTURE FUNDS

Funds in 2002

Fund name	Firm	Location
MPM Bioventures III	MPM Capital	Boston, MA
Versant Affiliates Fund II - A	Versant Ventures	Menlo Park, CA

All but two

ARE GONE

Source: 2003 E&Y Biotech Report (E&Y and Venture One data)

...LPs LEFT THE SECTOR

U.S. VC FUNDRAISING BY LPs

U.S. Venture Capital Funds Raised, By Year

Source: Pitchbook

THIS TIME IS DIFFERENT... WE HOPE

- Deeper equity capital markets, with broader private and public participation
- Many more successful mid & large biotechs, creating more opportunities for generalist investors
- Scientific breakthroughs with translational potential as rich as ever
- Industry structure favors external innovation and biotech origination
- Fewer tourist LPs to the asset class today; institutional LPs generally take longer term view across cycles with top tier funds

Disclosure

STIFEL | Healthcare

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