Biopharmaceutical Sector

Update – Nov 4, 2024

STIFEL | Healthcare

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787 7th Avenue, New York NY 10019, +1 (212) 887-7777
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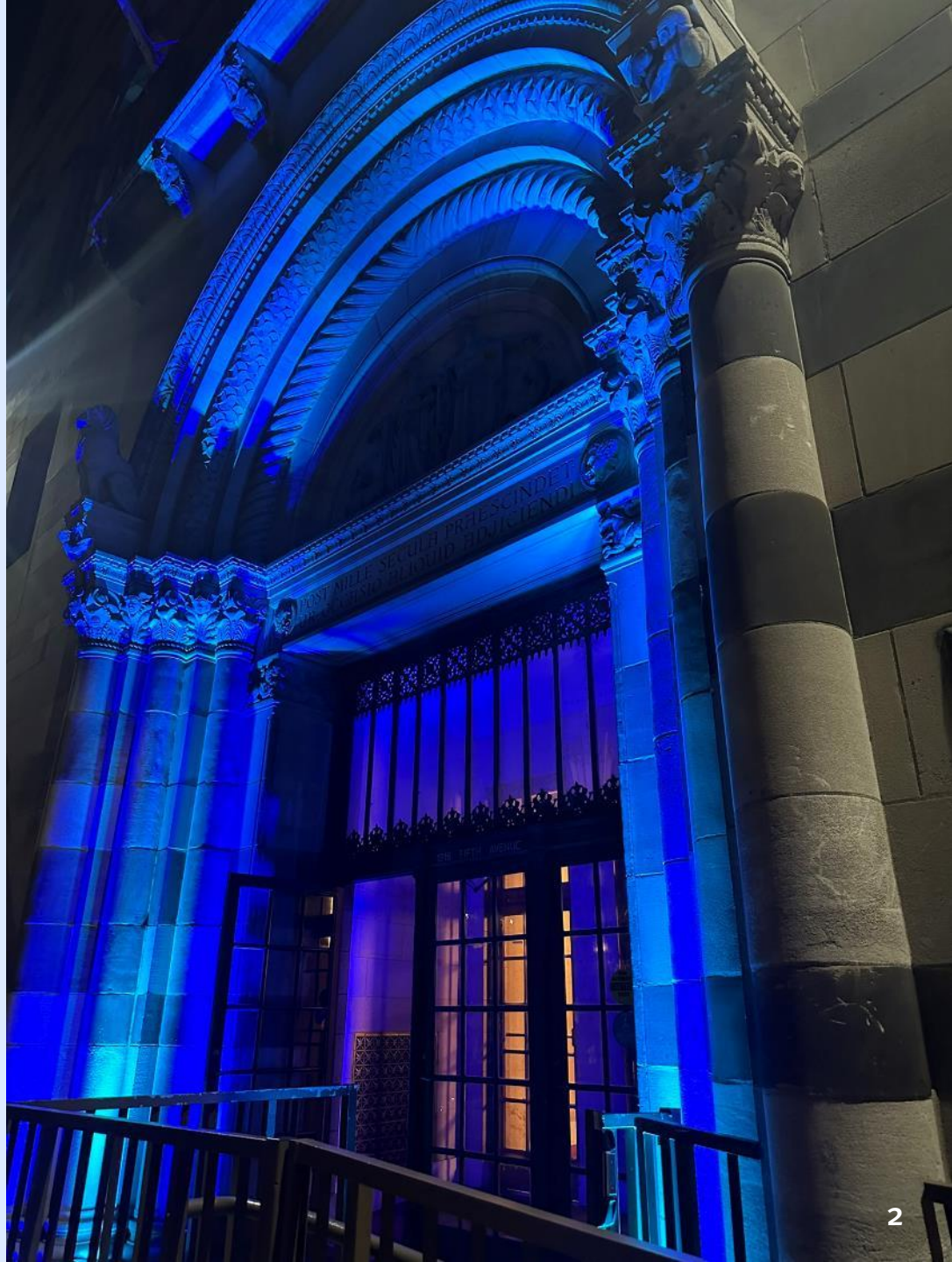

Entrance to the New York Academy of Medicine, October 2024

Past Issues

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

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Autumnal Ivy at the Biblioteken vid Lund Universitet, Home of One of the World's Best Collections of Medical History Books, Oct 2024.

Join Us at Biotech Hangout This Friday

And meet us at Bio-Europe starting next Monday

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

The week of Nov 4 will feature over 5,000 biopharma professionals in Stockholm for Bio-Europe. We'd love to meet you there.

https://informaconnect.com/bioeurope/

To meet with Stifel @ Bio-Europe
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Macro and The U.S. Presidential Election

Japanese Newspaper Portrayal of U.S. Election Politics, October 2024

U.S. Economy Added Just 12,000 Jobs in October

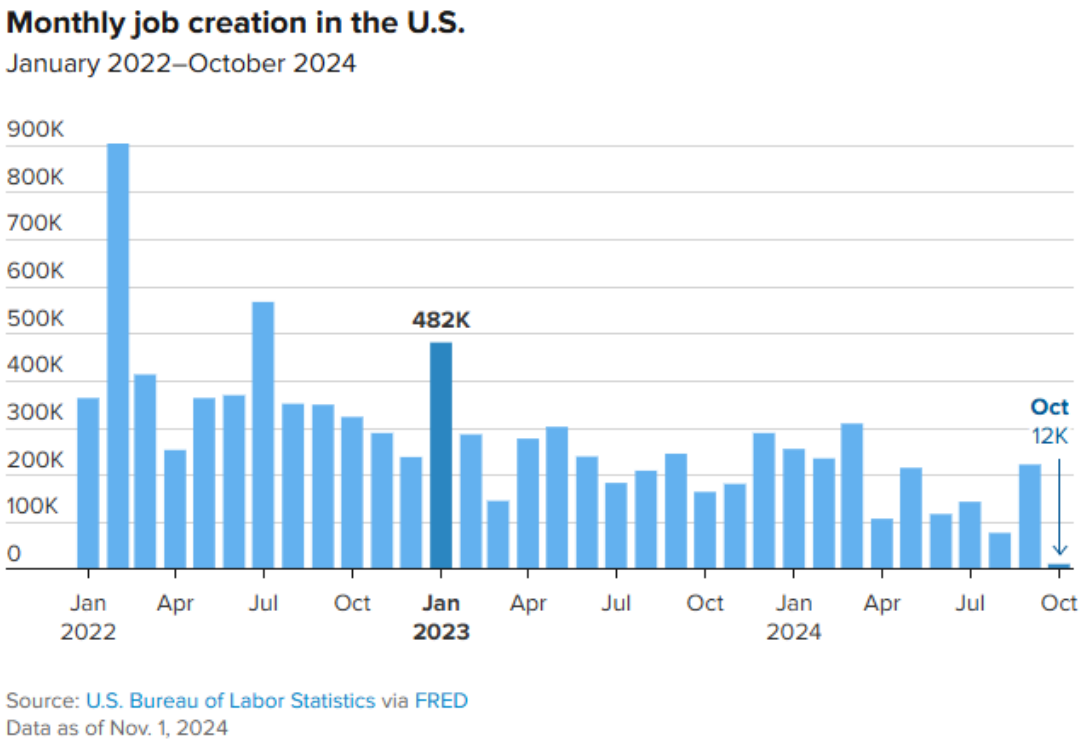
By Mark Niquette and Jarrell Dillard, *Bloomberg,* Oct 31, 2024 (excerpt)

Applications for US unemployment benefits fell last week to their lowest since May as southeastern states continued to recover from the impact of two severe storms.

Initial claims decreased by 12,000 to 216,000 in the week ended Oct. 26. The median forecast in a Bloomberg survey of economists called for 230,000 applications.

Continuing claims, a proxy for the number of people receiving benefits, fell to 1.86 million in the previous week, according to Labor Department data released Thursday.

Claims data this month have been even more volatile than usual after Hurricanes Helene and Milton devastated parts of the South and shut down businesses. In addition, a weeks-long strike at Boeing Co. probably led idled suppliers to furlough workers, further obscuring underlying trends in the labor market.



Source: https://www.bloomberg.com/news/articles/2024-10-31/us-initial-jobless-claims-fall-to-five-month-low

Market Down a Bit Last Week Despite Jobs News

Hakyung Kim and Alex Kim, *CNBC,* Nov 1, 2024 (excerpt)

Stocks rallied Friday to kick off November as Amazon led big technology stocks into the green and traders looked past a disappointing jobs report.

Meanwhile, the jobs report released Friday showed the U.S. economy added just 12,000 jobs in October, far below the Dow Jones estimate of 100,000. This marked the weakest level of jobs creation since December 2020. The unemployment rate held at 4.1%, in line with estimates. However, traders were not reacting too much to the jobs figures, believing the dismal data was affected by hurricanes and a Boeing strike.

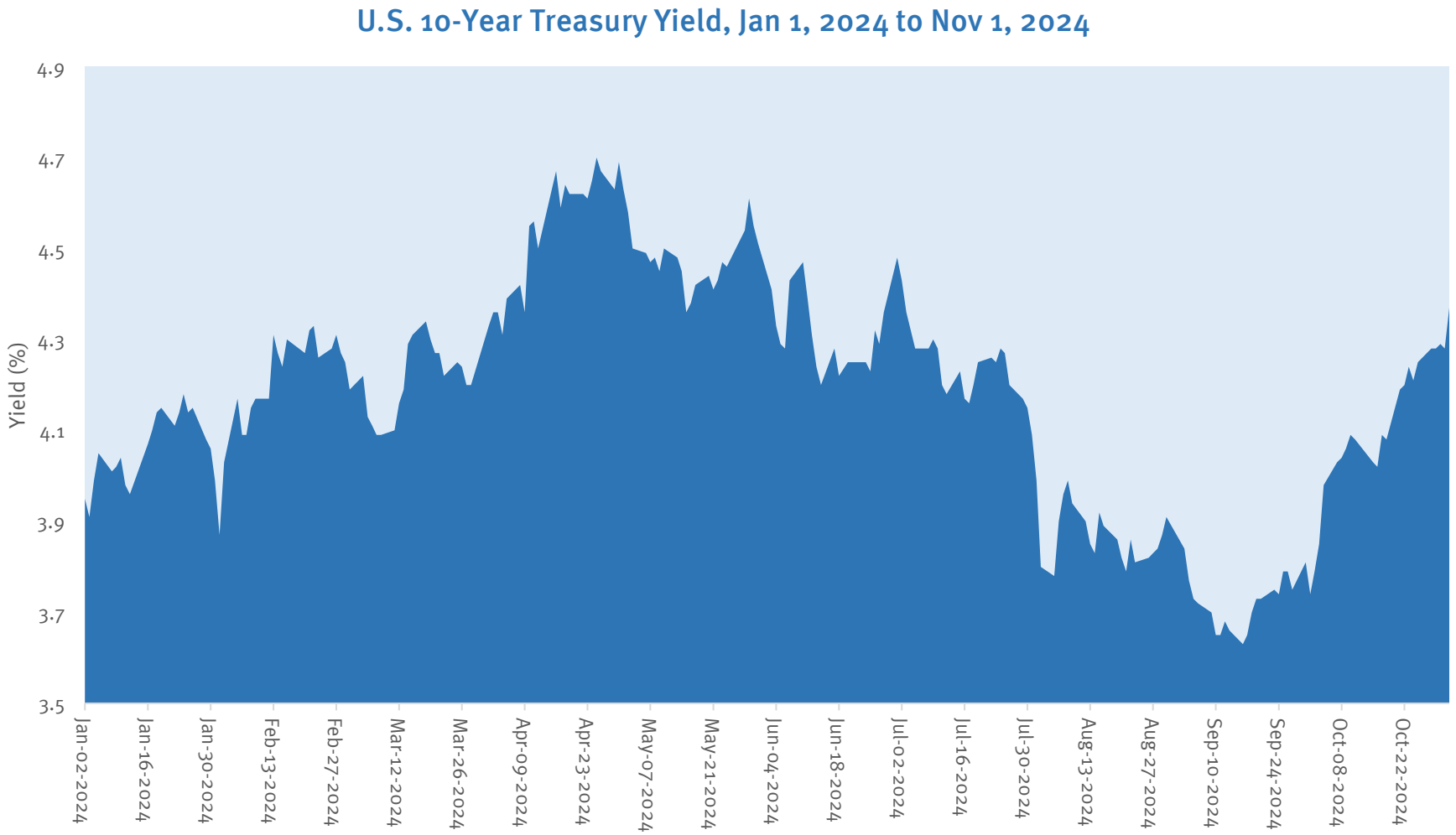
"Friday's jobs report showed that the labor market decelerated quite significantly in October compared to September," said Clark Bellin, president and chief investment officer at Bellwether Wealth. "But this was a noisy number largely due to hurricanes and labor strikes, so it's unlikely that this weakness is going to cause the Federal Reserve to pivot away from its expected 25 basis point rate cut at the November meeting."

In addition to the U.S. presidential election on Nov. 5., which has led to elevated volatility, investors are also looking toward the Fed's two-day policy meeting on Nov. 6-7.

The major averages are wrapping up a choppy week. The S&P 500 lost 1.4% in the period, while the Nasdaq slid 1.5%. Postearnings slumps in Microsoft and Meta Platforms weighed on the indexes. The 30-stock Dow inched down 0.2% week to date.

Source: https://www.bloomberg.com/news/articles/2024-10-31/us-initial-jobless-claims-fall-to-five-month-low

Treasury Yields Jumped Last Week Despite Weak Jobs News



The ongoing rise in Treasury yields is not good for biotech and also bad news for IPO/follow-on market momentum.

Investors are nervous about deficits and spend going into next week's election. The fear is that one party gets control of the White House and both houses of Congress. Investors worry that both parties have spending tendencies that will be bad for deficits and Treasuries.

538: U.S. Presidential Election Looks Incredibly Close

G. Elliott Morris, *538*, Nov 2, 2024 (excerpt)

Now that we are in the closing days of the 2024 presidential race, pollsters have started releasing their final readings of the campaign. They have mostly been a mixed bag. On Friday, Marist College released their highly-anticipated final polls across the Midwestern states, finding Vice President Kamala Harris ahead of former President Donald Trump by 3 points in Michigan, 2 points in Pennsylvania and 2 points in Wisconsin. That would be good news for Harris if those were the only polls released this week, but they weren't: An Echelon Insights survey found Trump up 5 points in the Keystone State, and CNN/SSRS has the former president up by 1 in Georgia. In aggregate, this has been enough to push our model modestly back in Harris's direction. Currently, our forecast gives Trump a 50 out of 100 chance of winning the election, and gives Harris a 49 out of 100 chance.

Still, the closeness of the race bears repeating what has become something of a mantra here at 538 recently: A close race in the polls does not necessarily mean the outcome will be close. All seven swing states are still within a normal polling error of going to the candidate who is currently "losing"in each. While the polls have identified a close race, our model shows what you should expect if those polls are off.

538's forecast is based on a combination of polls and campaign "fundamentals," such as economic conditions, state partisanship and incumbency. It's not meant to "call" a winner, but rather to give you a sense of how likely each candidate is to win.

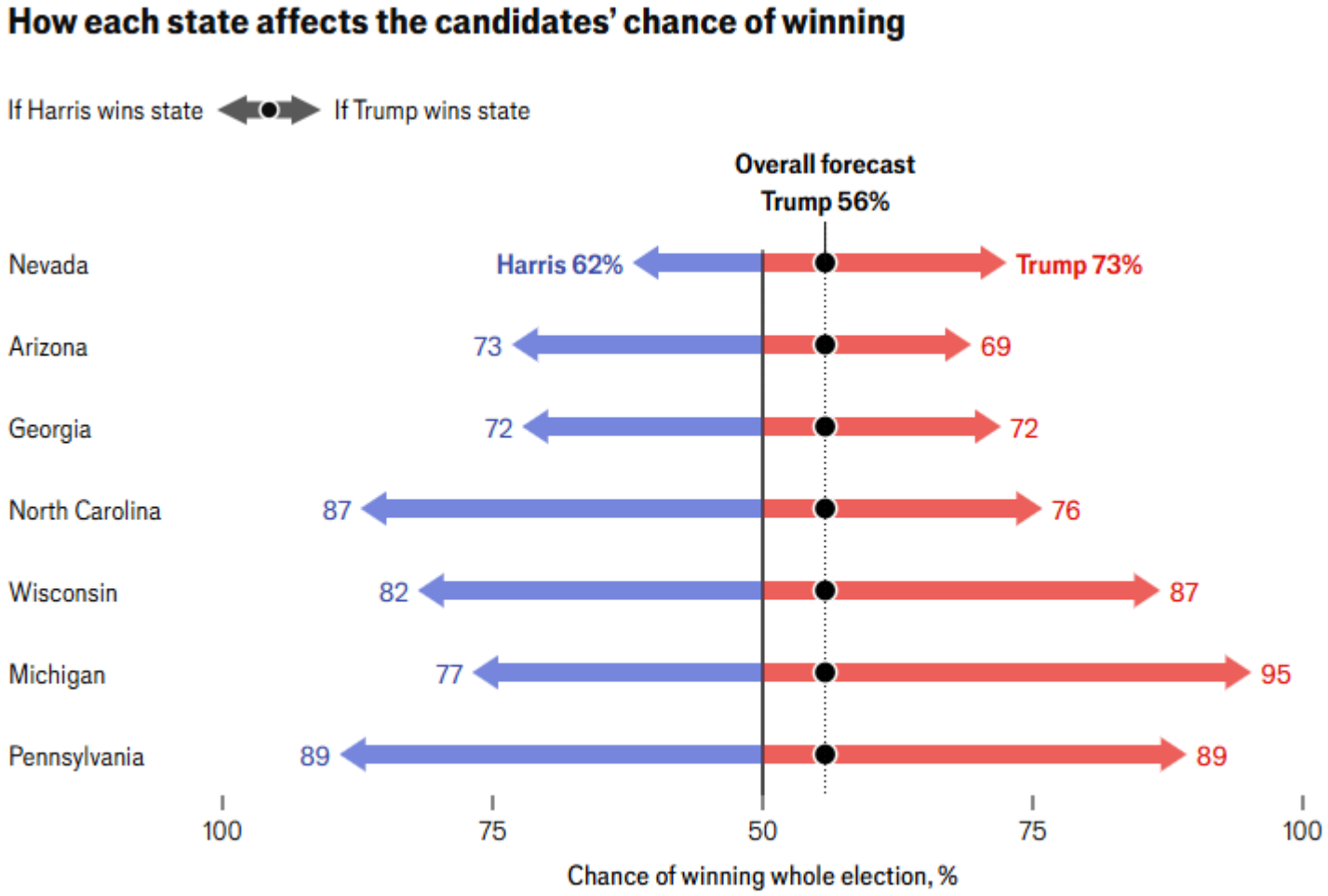
Source: https://projects.fivethirtyeight.com/2024-election-forecast/

Seven Key States Will Likely Determine The Election Outcome

The Economist, Oct 29, 2024 (excerpt)

Our first chart uses data from our presidential forecast model to show what each swing state tells us about the 270 electoral-college votes needed to win the election. The model produces 10,001 simulations of the election to predict which candidate is most likely to win. By our calculations, Pennsylvania is the most important state for both candidates (Mr Trump won Pennsylvania in 2016, but it flipped to Joe Biden in 2020). Ms Harris and Mr Trump both win in 89% of our simulations when they take the Keystone State's 19 electoral votes.

Mr. Trump has even better odds (95%) when he wins Michigan, but he has more alternative routes to the presidency without Michigan than without Pennsylvania. Other swing states are less influential: Ms Harris and Mr Trump win the election in only 62% and 73% of simulations, respectively, when they win Nevada, a state with only six electoral votes.



Source: https://www.economist.com/interactive/graphic-detail/2024/10/29/our-guide-to-how-trump-or-harris-might-win-the-election

Harris, Trump Hold Narrow Leads in Key Swing States: Poll

Tara Suter, *The Hill*, Nov 3, 2024 (excerpt)

Vice President Harris and former President Trump hold leads in different important swing states, according to new polling.

The polling from The New York Times/Siena College and The New York Times/Philadelphia Inquirer/Siena College, released Sunday, found Harris garnered 49 percent support from likely voters to Trump's 46 percent support in Nevada; 48 percent support from likely voters to Trump's 46 percent in North Carolina; 49 percent support from likely voters to Trump's 47 percent in Wisconsin; and 48 percent support from likely voters to Trump's 47 percent in Georgia.

Trump came out ahead in the polling in Arizona, garnering 49 percent support from likely voters to Harris's 45 percent, while the two were tied at 47 percent support from likely voters in Michigan and 48 percent support from likely voters in Pennsylvania. **Harris leads in the seven battleground states overall by 1 point, garnering 48 percent support from likely voters to Trump's 47 percent support.**

The Times/Siena polling also showed good news for Democratic Senate candidates in the swing states, with 50 percent of the likely voters in the seven states saying they would "be more likely to vote for" a Democrat in the race versus 45 percent saying they would be more likely to vote for a Republican.

The Times/Siena and Times/Inquirer/Siena polling took place between Oct. 24 and Nov. 1, featuring 7,879 voters and a margin of sampling error of plus or minus 1.3 percentage points, with each state having around a plus or minus 3.5 percentage point margin of sampling error.

Source: https://thehill.com/homenews/campaign/4968198-harris-trump-hold-narrow-leads-in-key-swing-state-poll/

How Will the Presidential Election Impact Biopharma?

Greg Slabodkin, *Biospace*, Oct 29, 2024 (excerpt)

While some analysts say Donald Trump is a wild card when it comes to drug pricing, many argue his presidency would be more positive for the industry overall, as Kamala Harris has her price-cutting sights squarely on Big Pharma.

While the political contest is too close to call, analysts and stakeholders have weighed in on the high-profile biopharma issues—including drug pricing reforms—that could figure prominently in the new administration.

Under a second Trump presidency, the market can rest assured that the Inflation Reduction Act (IRA) will not be expanded—in fact, there is speculation it may even be repealed—and that the Federal Trade Commission (FTC) will shift its focus away from biopharma, and drug pricing reform will target pharmacy benefit managers (PBMs), according to Seigerman and Biliouris.

On the other hand, Harris in her economic plan makes the case that both PBMs and Big Pharma are to blame for inflated prescription drug prices, and her administration "will crack down on pharmaceutical companies that block competition and abusive practices by pharmaceutical middlemen who squeeze small pharmacies' profits and raise costs for consumers."

While Trump hasn't made drug pricing a focus of his 2024 campaign as he did in the run-ups to the 2016 and 2020 presidential elections, Kirsten Axelsen, a nonresident fellow at the American Enterprise Institute, pointed out to BioSpace that "Trump is one of the few Republicans who supported price controls on drugs—that has not typically been a Republican stance." It's a sentiment echoed by John Stanford, executive director of Incubate, a Washington-based coalition of life sciences venture capitalists. Stanford told *BioSpace* that in a second presidential term, Trump could make cuts to drug pricing a part of his agenda. "I think he's shown a willingness to use any tool in the toolbox to react to populist priorities," Stanford said. "It's hard to cross anything off the [policy] menu with him."

Another open question regarding a Trump presidency is whether he would seek to repeal the IRA. Harris cast the tie-breaking vote in the Senate for the bill and President Joe Biden signed the IRA into law in 2022—the Biden-Harris administration's crowning legislative achievement, empowering Medicare for the first time to negotiate prescription drug prices.

Project 2025, a blueprint for a potential second Trump term drafted by the conservative Heritage Foundation think tank, calls for repealing the IRA. According to Project 2025's chapter on the Department of Health and Human Services (HHS), the IRA's Medicare Drug Price Negotiation Program "replaced the existing private-sector negotiations in Part D with government price controls for prescription drugs" that "will limit access to medications and reduce patient access to new medication."

If Trump's policy priorities when it comes to drug pricing appear to be all over the map, Harris' economic plan, A New Way Forward for the Middle Class, has Big Pharma squarely in its sights. The Harris plan calls for accelerating the speed of Medicare prescription drug negotiations by expanding the IRA's cost-saving provisions to benefit all Americans. "Harris will allow Medicare to accelerate the speed of negotiations so the prices of more drugs come down faster."

Source: https://www.biopharmadive.com/news/election-trump-harris-pharma-policies/729835/

Kamala Harris Advocates a Cap on Out-of-Pocket Drug Costs

Jessica Corbett, *Common Dreams*, Nov 1, 2024 (excerpt)

As Republican former U.S. President Donald Trump threatens to "terminate" a 2022 law that cut prescription costs for seniors, his Democratic opponent in next week's election, Vice President Kamala Harris, is pushing for an expansion of the policy that could save Americans billions of dollars, according to research released Friday.

Two years ago, President Joe Biden signed the Inflation Reduction Act (IRA), capping annual out-of-pocket costs for patients with Medicare Part D; it's currently around $3,500 but set to drop to $2,000 next year. The Biden White House's budget for fiscal year 2025 and the Harris campaign have both advocated for extending that cap to people with private health insurance.

The government watchdog group Public Citizen found that if implemented in 2022, "a $2,000 annual cap would have reached more than 900,000 patients with private insurance, saving them a total of $2.78 billion, equating to over $3,000 in savings per patient."

Public Citizen co-president Robert Weissman said in a statement Friday that "no one should ever have to choose between taking their medicine and putting food on the table."

Source: https://www.commondreams.org/news/us-prescription-drug-prices

Kamala Harris Cool on FTC Head Lina Khan

Brendan Bordelon and Adam Cancryn, *Politico*, Oct 24, 2024 (excerpt)

Vice President Kamala Harris has declined to appear with Khan or campaign on her energetic antitrust agenda — much less defend the FTC chair against a chorus of Silicon Valley donors calling for her head, or Khan's GOP critics on Capitol Hill.

Khan's aggressive push to unwind monopolies and break up market concentration, particularly in the tech sector, has vaulted her to a prominence rarely enjoyed by an FTC chair or other agency heads. But it's also splitting the Democratic Party on both substance and tactics in the final days of the presidential campaign.

Wealthy Harris supporters, including billionaire tech investor Mark Cuban and LinkedIn co-founder Reid Hoffman, have waged a high-volume campaign against Khan in the hope that Harris will fire her — and in the process, signal that her administration will take a more business-friendly bent than President Joe Biden's.

"When she won't defend Biden's record on antitrust, or defend Khan against the attacks by the billionaire donors — guys like Reid Hoffman, who've basically been calling for Khan's head — it kind of zaps the life out of the progressive base," said Hal Singer, an economist at the University of Utah and director of the Utah Project, an institute focused on antitrust and consumer protection.

"The anti-corporate left overestimates how big its voter support is," Kovacevich said. He told POLITICO that the Biden administration "got sideways with the median voter on the economy," and that Harris is looking to attract moderates repulsed by Trump but concerned that she's an economic radical.

"I believe that she's saying these things and doing these things — talking about business in a different way — because that's what swing voters want to hear," Kovacevich said.

Harris' progressive critics largely agree that the vice president's refusal to embrace Khan is tied to her high-profile plan to woo "moderate Republicans." But they fear her campaign may be misreading the moment.

Source: https://www.politico.com/news/2024/10/24/kamala-harris-lina-khan-00185345

RFK Jr. Set for Major Food, Health Role in Potential Trump Administration

Dan Diamond, Lauren Weber, Josh Dawsey, Michael Scherer and Rachel Roubein, *Washington Post*, Nov 2, 2024 (excerpt)

Robert F. Kennedy Jr. is poised to have significant control over health and food safety in a potential Trump administration, with discussions about some Cabinet and agency officials reporting to him, according to four people familiar with the planning process who spoke on the condition of anonymity to detail private conversations.

Kennedy has been privately meeting with Trump transition officials to help draw up an agenda for a new administration, which could involve the longtime anti-vaccine activist taking a role as a White House czar rather than attempting to win Senate confirmation to lead an agency, the people said

“The president has asked me to clean up corruption and conflicts at the agencies and to end the chronic disease epidemic,” Kennedy said in an interview Wednesday. “He wants measurable results in two years and to return those agencies to their long traditions of gold-standard evidence-based science and medicine.”

But Kennedy’s rising influence was reflected Wednesday night when Howard Lutnick, co-chair of the Trump transition team, made a startling admission during an appearance on CNN: He had come to doubt the power of vaccines, after a 2½-hour conversation with Kennedy.

“Why do you think vaccines are safe? … They’re not proven,” Lutnick said, repeating Kennedy’s debunked claims about vaccines’ link to autism and insufficient data on their harms. He added that Kennedy wants to study the data himself and make recommendations. “I think it’ll be pretty cool to give him the data. Let’s see what he comes up with,” Lutnick said.

Source: https://www.washingtonpost.com/politics/2024/10/31/rfk-trump-administration-health-food-safety/

TOOTHACHE TROUBLES

TRUMP'S HEALTH PICK RFK JR. TOUTS REMOVING FLUORIDE FROM WATER

"Fluoride is an industrial waste associated with arthritis, bone fractures, bone cancer, IQ loss," the oft-health conspiracy theorist claims

Althea Legaspi, *Rolling Stone*, November 2, 2024

During Donald Trump's second of three rallies on Saturday (with six total planned on the last weekend before Election Day), he told the audience in Salem, Virginia his pick for leading up health in his administration should he return to the White House would be Robert F. Kennedy Jr. Meawhile, RFK Jr. was tweeting how the administration would plan to remove fluoride from the public water system on Day One should Trump win the election.

"On January 20, the Trump White House will advise all U.S. water systems to remove fluoride from public water," RFK Jr. posted on X, formerly Twitter. "Fluoride is an industrial waste associated with arthritis, bone fractures, bone cancer, IQ loss, neurodevelopmental disorders, and thyroid disease. President @realDonaldTrump and First Lady @MELANIATRUMP want to Make America Healthy Again." RFK Jr.'s tweet linked to a video from a lawyer involved in a long-running lawsuit, which did recently find some concern over fluoride, though more research has been recommended. In September, a federal court in California ruled against the EPA, ordering it to take action over potential health risks from its current fluoride level recommendations.

Source: https://www.rollingstone.com/politics/politics-news/trump-health-pick-rfk-jr-removing-fluoride-from-water-1235151497/

Concerns Expressed on Potential RFK Role in Trump Administration on Last Friday's Biotech Hangout

Biotech Hangout ✓
@BiotechCH

Kicking off today's show, special guest @steveusdin1 from @BioCentury shares his thoughts on the political climate and RFK Jr.'s potential impact on healthcare. "FDA and public health have become far more politicized. Trump and people around him don't want strong independent agency heads. Even if RFK Jr. doesn't have a powerful job, he could still have influence. He will likely be in the White House and have the ear of the president." #BiotechHangout

12:13 PM · Nov 1, 2024 · **411** Views

.@MatteisPaul wonders if certain biotech areas are particularly vulnerable to RFK Jr. and a Trump presidency. @steveusdin1 notes that vaccines, reproductive health, and neuropsychiatric diseases may be in the crosshairs. "It's more a general issue that will cut across areas if you see the FDA losing its independence and reputation for calling balls and strikes." #BiotechHangout

Switching over to a potential Harris victory, @steveusdin1 expects to see continuity at the FDA. "The bigger concerns would be around IRA and drug price controls, which depend a great deal on control of the house and senate." #BiotechHangout

Life Sciences Leaders Blast Possibility that Trump taps RFK Jr. to Run Public Health Agencies

Jonathan Saltzman, *Boston Globe*, Nov 2, 2024 (excerpt)

Prominent figures in Massachusetts' life sciences industry are decrying the possibility, which gained momentum this week, that Donald Trump might appoint Robert F. Kennedy Jr. to run a federal public health agency if the former president regains the White House. Kennedy, the scion of the famous Democratic political dynasty, has made headlines and drew considerable support in his recent presidential bid as an independent by championing conspiracy theories, including the discredited claim that childhood vaccines are linked to autism.

Several biotech executives say those views disqualify him for a job protecting public health, something Trump has signaled he is considering.

"It would be deeply concerning to have somebody who is so against science and truth and evidence in a leadership role related to the health of the American people," said John Maraganore, executive chairman of the newly launched Cambridge startup City Therapeutics. Maraganore is the respected former founding chief executive of Cambridge-based Alnylam Pharmaceuticals, one of the state's biggest homegrown biotech employers, which uses gene-silencing technology to treat genetic disorders.

Trump has pledged that Kennedy would be involved in his administration and has named him to the Republican's transition team. Trump hasn't specified a potential job for Kennedy, who suspended his presidential campaign in August and endorsed the candidate. Kennedy's siblings decried the endorsement as "a betrayal of the values that our father and our family hold most dear."

Steven Holtzman, the retired chief executive of Decibel Therapeutics and a former executive vice president at Cambridge-based Biogen, said the FDA is "the paradigm of a regulatory authority driven by science." "The politicization of the Agency or ceding its leadership to individuals who subscribe to 'populist' anti-science views and rhetoric would be a tragedy," Holtzman said in an email.

Source: https://www.bostonglobe.com/2024/11/01/business/rfk-trump-vaccine-cdc-fda

Our View of How the Candidates Stack Up Relative to Biopharma Interests

The three most important biotech issues are limiting the IRA, keeping the FDA strong and limiting FTC activism. Harris is most attractive on the FDA. Trump is most attractive on the IRA. Trump is somewhat more likely to restrain FTC activism although Harris does not appear to be an activist in this area.

Harris

Trump

	Harris	Trump
Inflation Reduction Act Walk-Back	★	★★★★
Keep a Strong and Independent FDA	★★★★★	★★
Restrain Medicare Advantage / Part D	★★★★	★★
Restrain FTC Activism on M&A	★★★	★★★★★
Regulate PBMs	★★★★	★★
Limit Corporate / Individual Taxes	★	★★★★
Prevent IP March-In Rights	★★★	★
Maintain Strong NIH/ARPA-H Spend	★★★★★	★★★

Biopharma Market Update

Meeting Room at 5Y Capital, Shanghai China (https://www.5ycap.com/en/), October 2024

The XBI Closed at 99.3 Last Friday (Nov 1), Up 2.2% for the Week

The XBI was up slightly last week ahead of the election. The XBI has been largely flat since July. We are hopeful that the market will be stronger after next week's election recedes.

Biotech Stocks Up Last Week

Return: Oct 24 to No 1, 2024

Nasdaq Biotech Index: +0.0%
Arca XBI ETF: +2.2%
Stifel Global Biotech EV (adjusted): +6.1%*
S&P 500: -1.4%

Return: Dec 29, 2023 to Nov 1, 2024 (YTD)

Nasdaq Biotech Index: +7.8%
Arca XBI ETF: 11.2%
Stifel Global Biotech EV (adjusted): +43.8%*
S&P 500: +20.1%

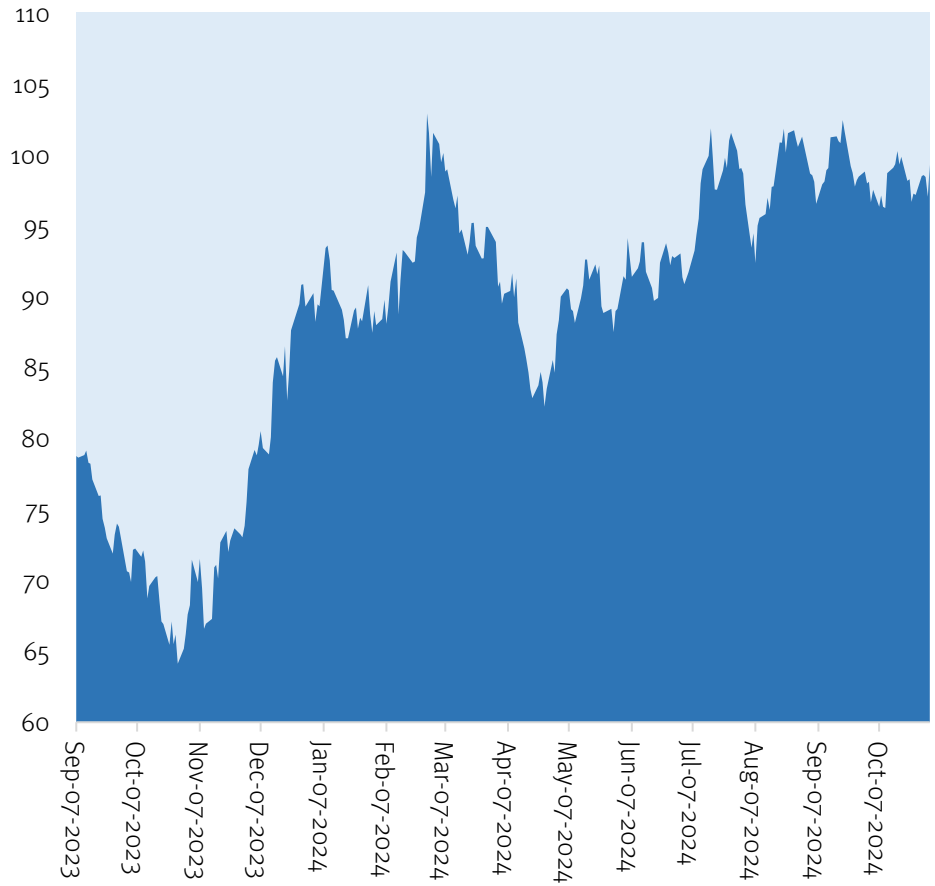
VIX Up

Sep 29, 2023: 17.3%
Dec 29, 2023: 12.45%
Mar 29, 2024: 13.0%
May 17, 2024: 12.0%
Aug 2, 2024: 23.4%
Sep 20, 2024: 16.1%
Oct 19, 2024: 18.0%
Nov 1, 2024: 21.9%

10-Year Treasury Yield Up

Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Mar 29, 2024: 4.20%
May 17, 2024: 4.42%
Aug 2, 2024: 3.80%
Sep 20, 2024: 3.73%
Oct 19, 2024: 4.08%
Nov 1, 2024: 4.28%

XBI, Sep 7, 2023 to Nov 1, 2024



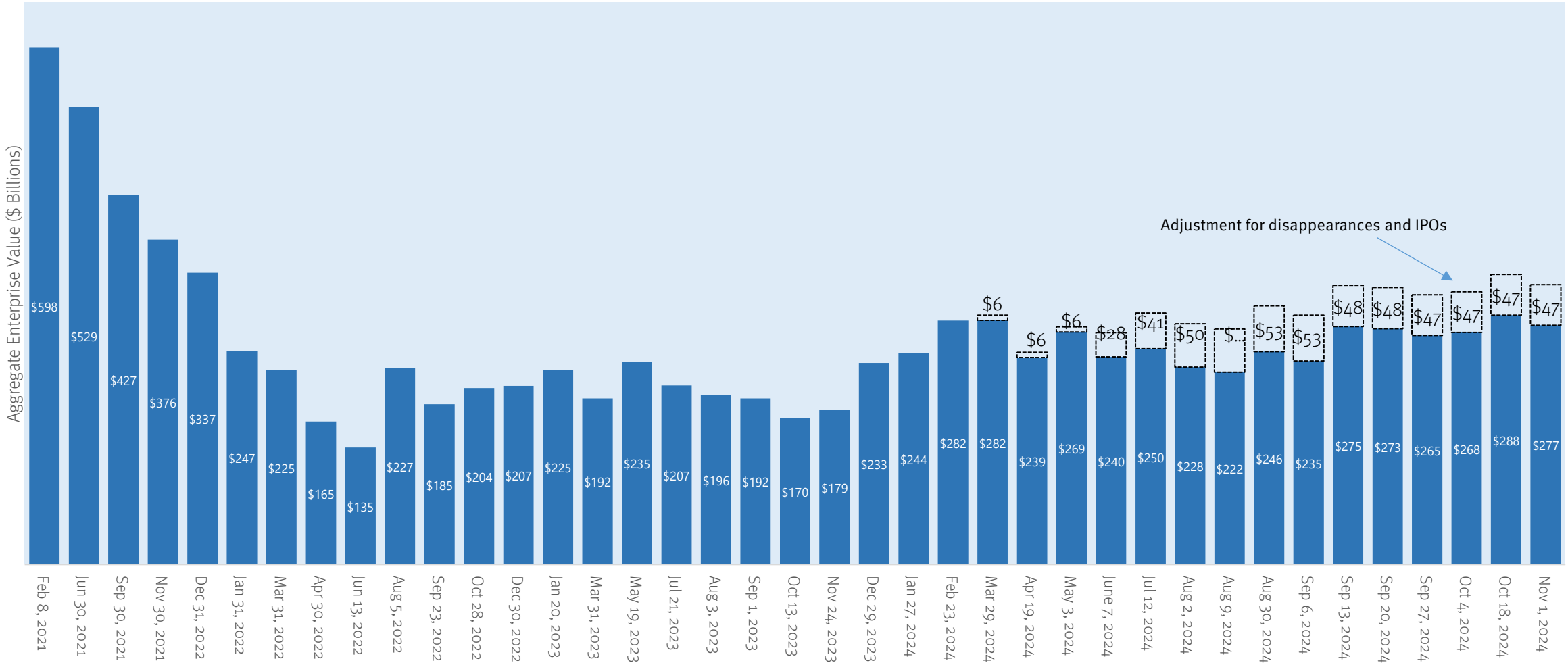
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down 4.1% in Last Two Weeks

Biotech stocks were down 4.1% in the last two weeks. On a disappearance adjusted basis, biotech is up 37.8% for the year to date (enterprise value). The last two weeks have not been great as Summit Therapeutics has shed value as new competitors in PD1 bispecific space have arrived.

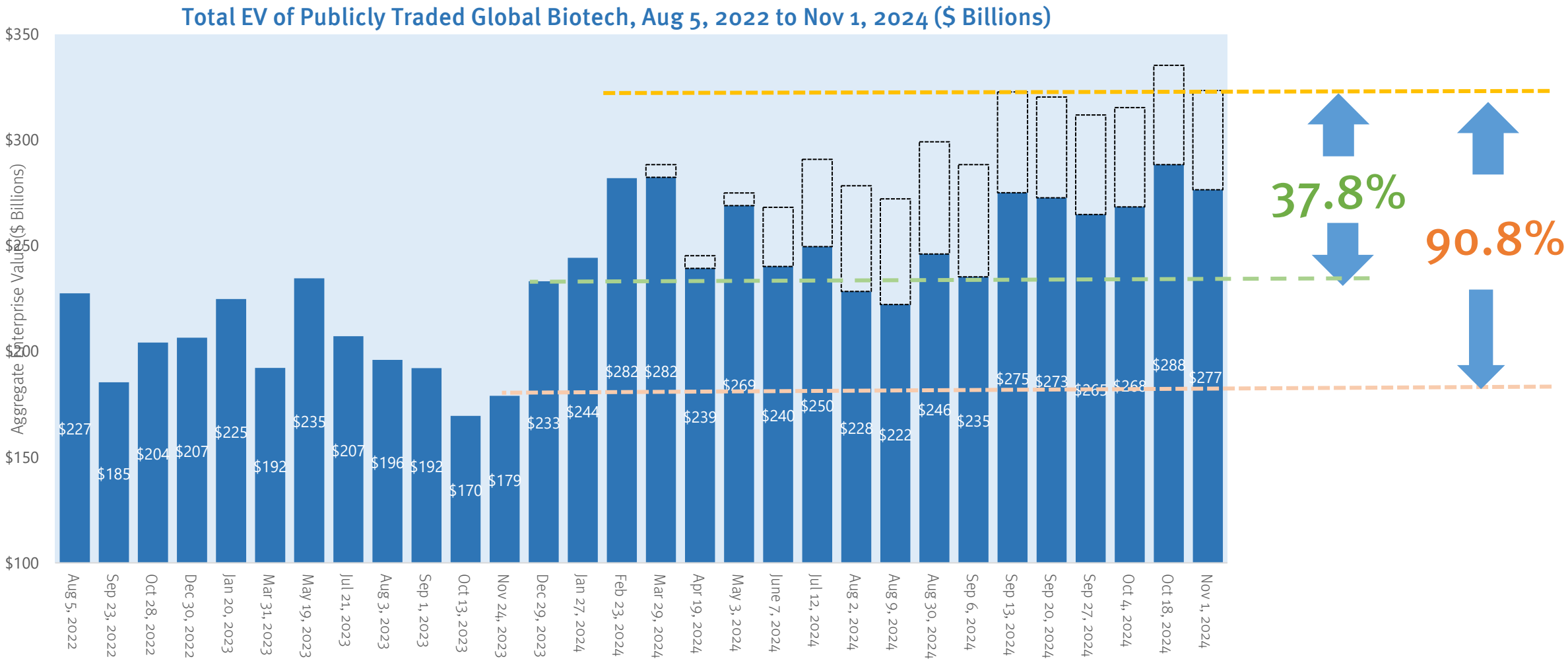
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Nov 1, 2024 ($ Billions)



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

Public Markets: Total Global Biotech Sector Up 37.8% This Year

On a disappearance adjusted basis, biotech is up 37.8% for the year to date (enterprise value). Over the last 12 months the market is up 90.8%. In contrast, the XBI is up 11.8% this year and 47% over the last twelve months.

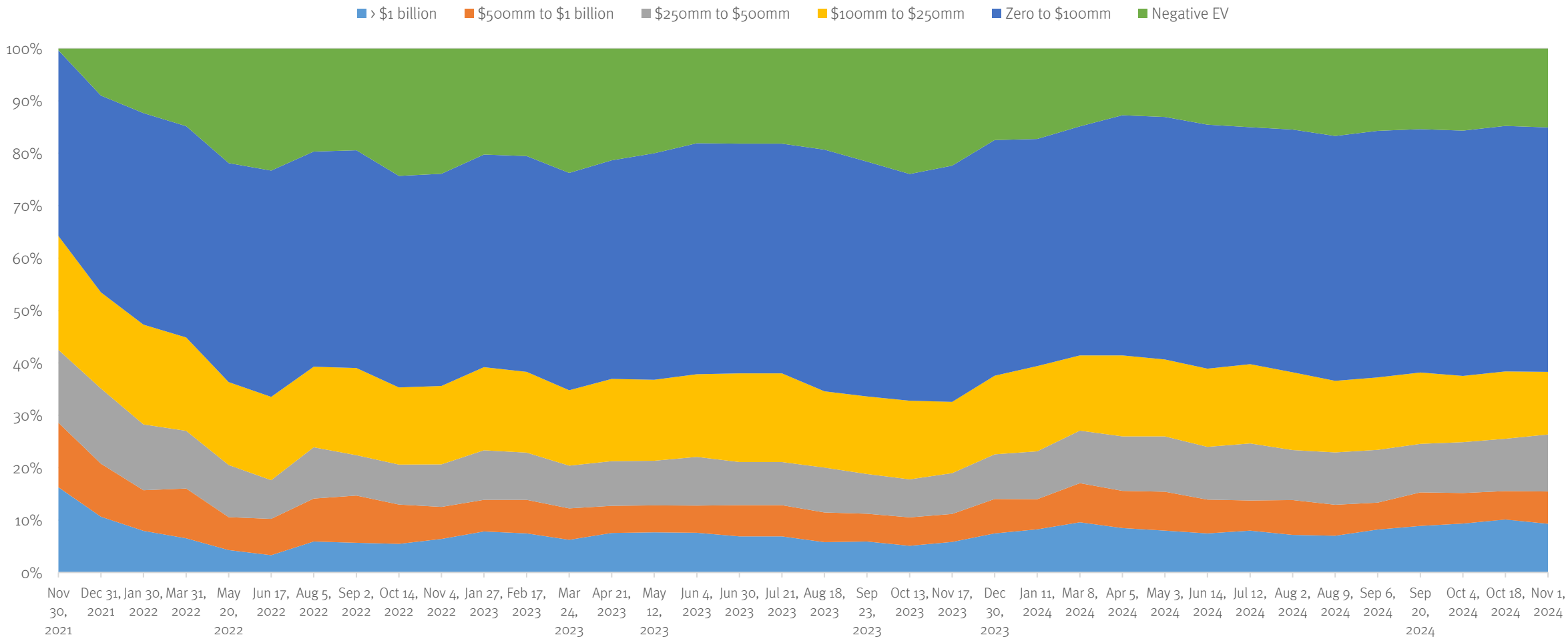


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Global Biotech Neighborhood Analysis

The population of high valued biotechs has shrunk meaningfully in the last few weeks. The number of negative EV biotechs has also shrunk meaningfully since August.

Global Biotech Universe by Enterprise Value Category, Nov 30, 2021 to Oct 18, 2024

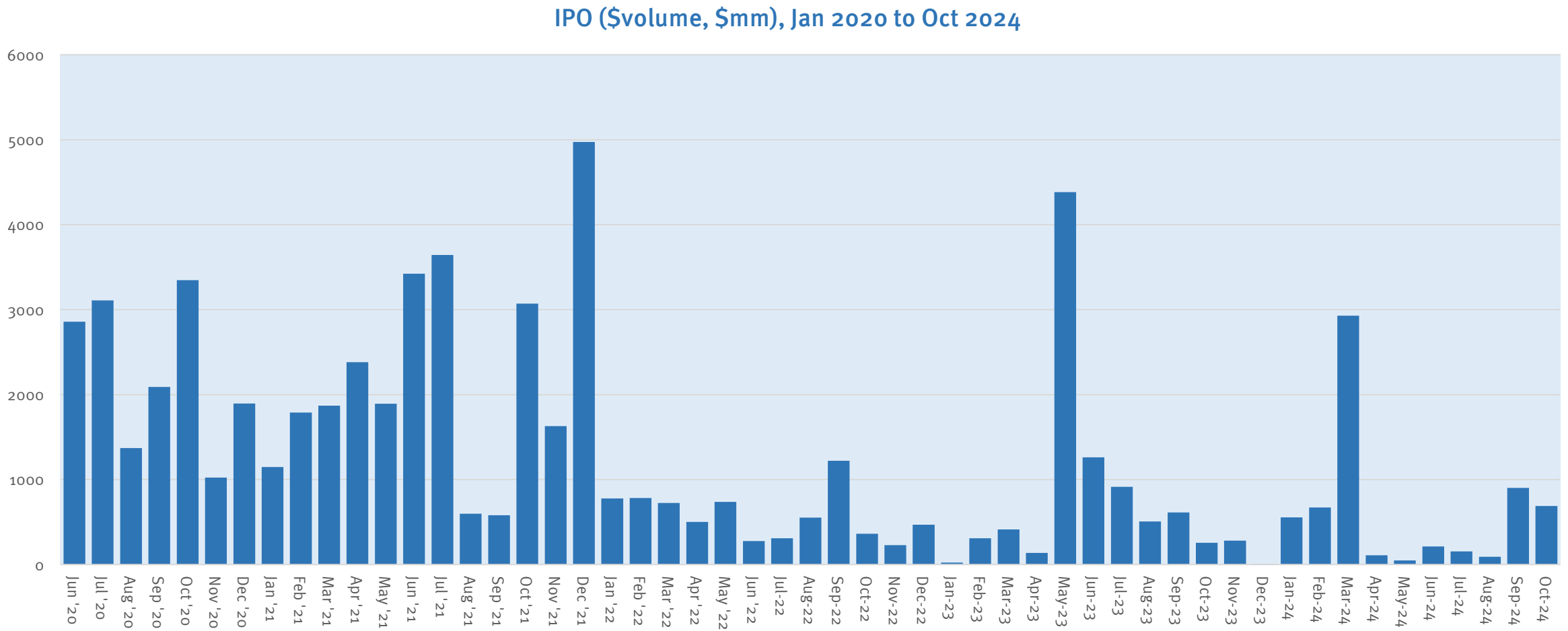


Source: CapitalIQ and Stifel analysis. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Capital Markets Update

IPO Market Activity Moderate in October 2024

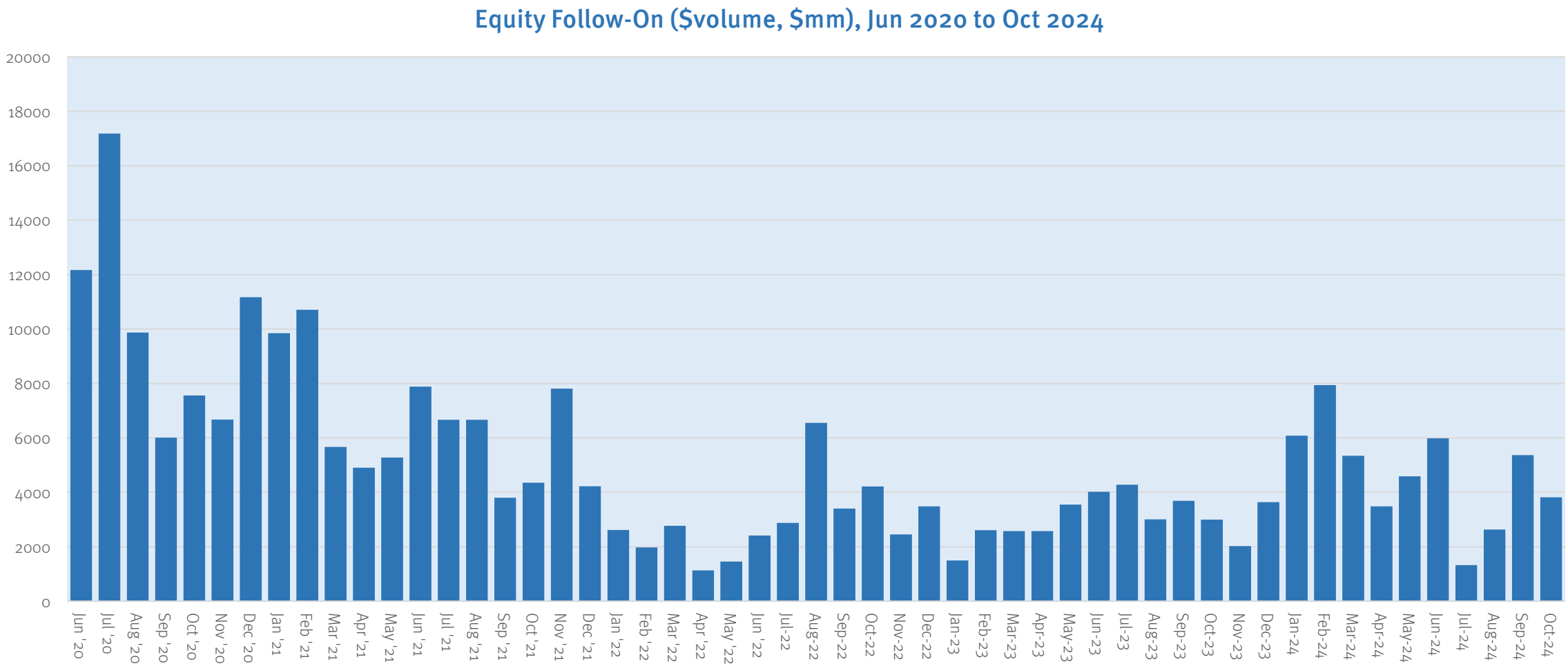
The IPO market perked up nicely after Labor Day and has remained open since then. October activity remained moderate compared to the Pandemic period but much stronger than earlier in 2024. The last two deals that exceeded $200mm were Septerna ($288mm raised on Oct 2) and Upstream Bio ($255mm raised on Sep 18). Septerna is up 18% from pricing. Upstream is up 46% from pricing.



Source: Data from CapitalIQ.

Equity Follow-On Market Steady

While not matching the torrid pace of early September, we saw $4 billion in follow-ons in October. This puts the market well above its pace from July and August of this year. We expect this market to pick up even further after the election.



Source: Data from CapitalIQ.

Stifel Active in Equity Capital Markets (IPO's, PIPE's and Follow-Ons)

STIFEL *Investment Banking* **SPOTLIGHT**

Announced Last Week

$200,000,000

CRESCENT BIOPHARMA

PIPE

Joint Placement Agent
Pending

$300,000,000

Jade BIOSCIENCES

PIPE

Joint Placement Agent
Pending

Announced in September

$575,000,000

Nuvalent

Follow-on Offering
Joint Bookrunning Manager
September 2024

$362,250,000

BICARA THERAPEUTICS

Initial Public Offering
Joint Bookrunning Manager
September 2024

$258,750,000

VIRIDIAN

Follow-on Offering
Joint Bookrunning Manager
September 2024

$230,000,000

RELAY THERAPEUTICS

Follow-on Offering
Joint Bookrunning Manager
September 2024

$187,680,000

MBX Biosciences

Initial Public Offering
Joint Bookrunning Manager
September 2024

$200,536,320

ORUKA THERAPEUTICS

PIPE
Joint Placement Agent
September 2024

Dollar volume represents full credit to each underwriter.
All transaction announcements above appear as a matter of record only.

Contact us for more information:

Mark Dempster
Managing Director
Life Sciences
mdempster@stifel.com

Matt Bouchard
Managing Director
Life Sciences
bouchardm@stifel.com

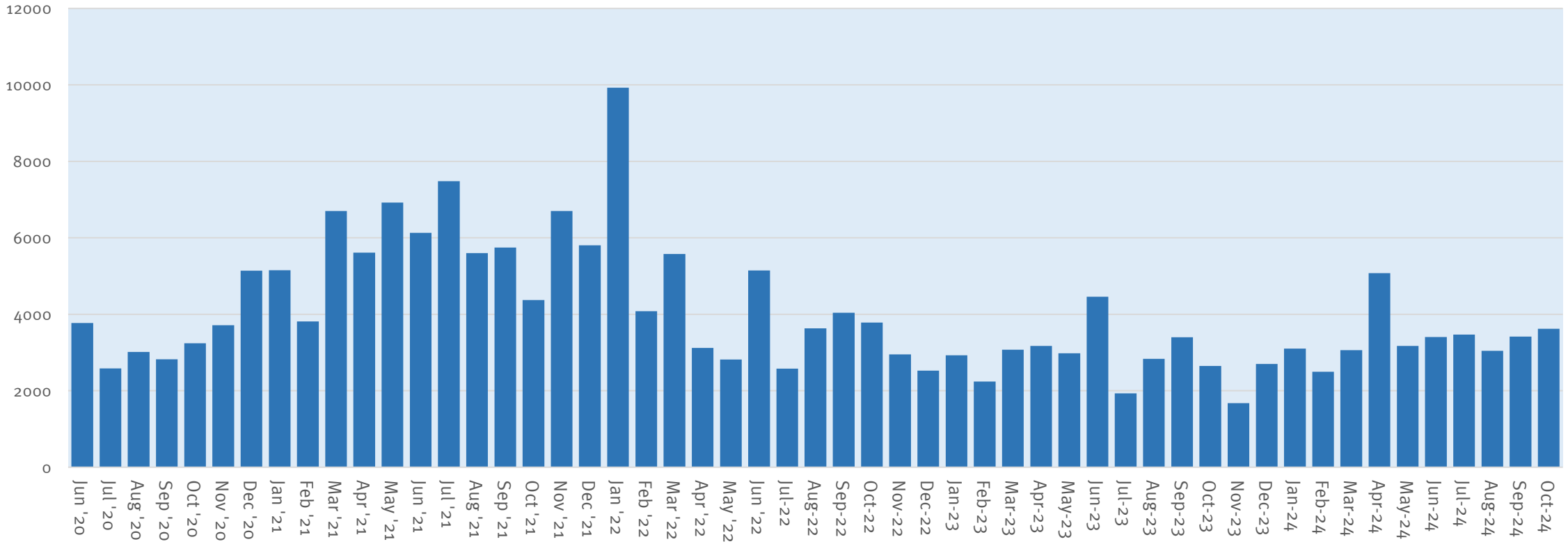
Ken Clausman
Managing Director
Equity Capital Markets
clausmank@stifel.com

Will McGrath
Managing Director
Life Sciences
wmcgrath@stifel.com

Private Venture Equity Market Robust in October 2024

Monthly volume of venture privates this year has averaged $4 billion (or roughly $50bn a year). October volume was right on track with this volume level. We are seeing a preponderance of larger raises getting done.

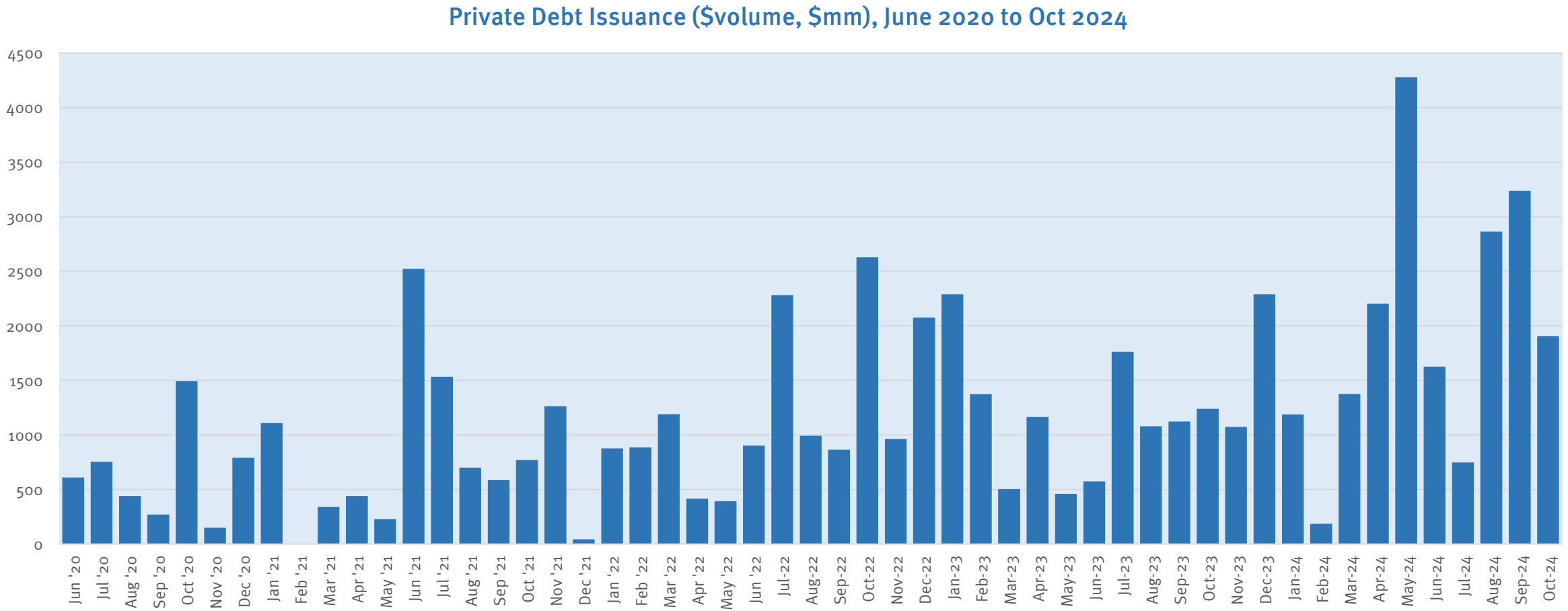
Monthly Private Equity Placement ($volume, $mm), Jun 2020 to Oct 2024



Source: Data from CapitalIQ, Crunchbase.

Biopharma Private Debt Market Cooled Down in October

The volumes in the private debt market have lightened up from the pace in August and September. Nonetheless, volumes remain quite elevated relative to the Q1 2023 to Q2 2024 period.

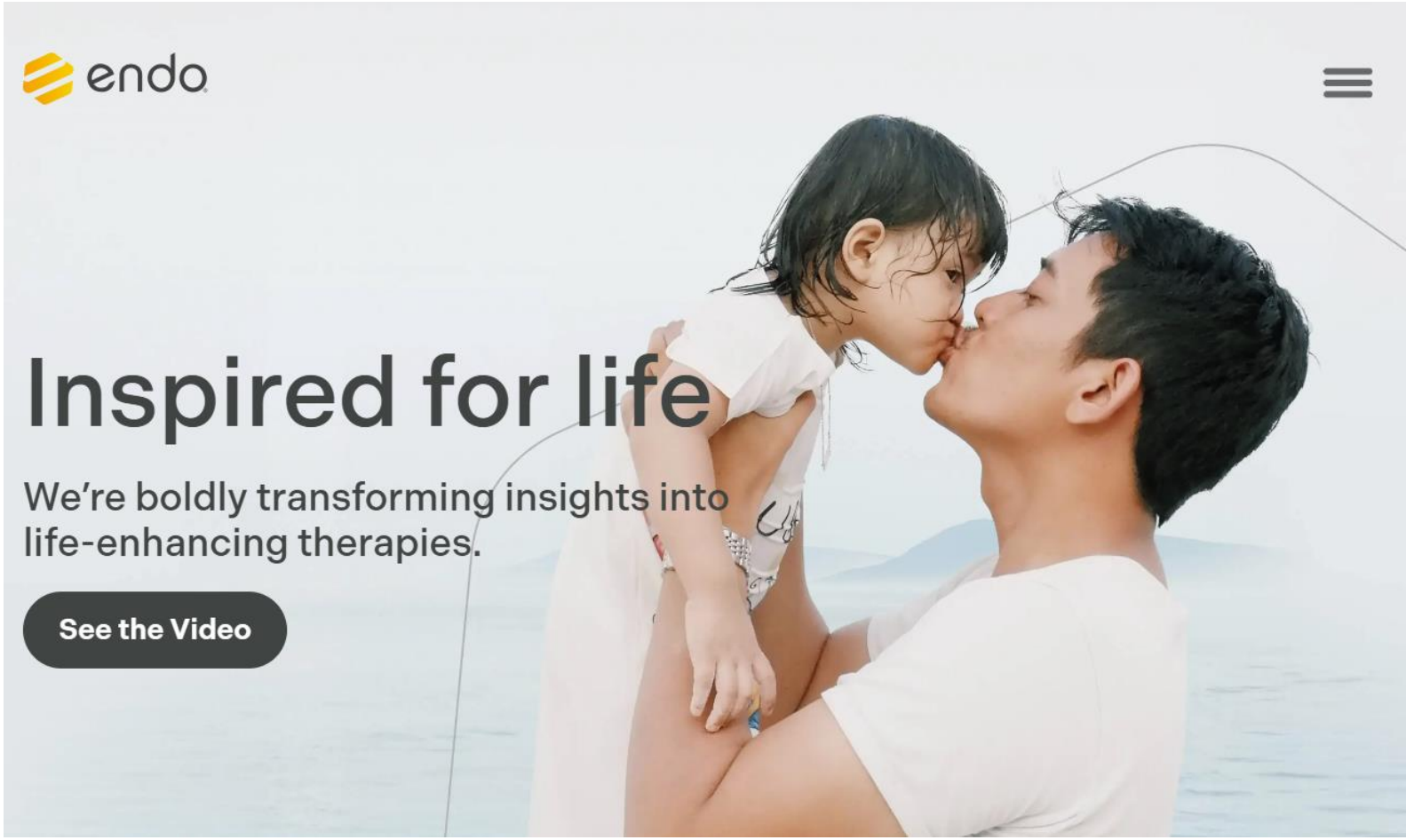


Source: Data from CapitalIQ, Crunchbase, Stifel research.

ENDO Reprices $1.5 Billion Term Loan Deal

MALVERN, Pa., Oct. 29, 2024

Endo, Inc. ("Endo" or the "Company") (OTCQX: NDOI), a diversified specialty pharmaceutical company transforming insights into life-enhancing therapies, today announced the Company has successfully completed the repricing of its $1.5 billion term loan (the "Term Loan") due 2031. The new applicable rate for the Term Loan is Term SOFR plus 400 basis points, which reduces the interest rate by 50 basis points. This transaction is expected to result in interest expense savings of approximately $8 million annually. There are no changes to the maturity of the Term Loan and all other terms remain substantially unchanged.



Source: https://investor.endo.com/2024-10-29-Endo-Announces-Successful-Term-Loan-Repricing

PL Developments Raises $500 Million in Debt

MIAMI and WESTBURY, N.Y., Oct. 28, 2024

PL Developments (PLD), a leader in the development, manufacturing, packaging, and distribution of consumer healthcare products, today announced two significant milestones: FDA approval for its Omeprazole OTC ANDA and the successful refinancing of its corporate debt.

In addition to this product milestone, PLD today announces the successful completion of its offer to exchange (the "Exchange Offer") $350,000,000 aggregate principal amount of its outstanding 7.750% Senior Secured Notes due 2025 (the "Old Notes") for new PIK Toggle Senior Secured Notes due 2029 (the "New Notes") in an aggregate principal amount of $368,550,000. This strategic move was made possible through improved financial performance and a collaborative effort with key stakeholders. The completion of the Exchange Offer enhances the company's financial flexibility and positions it for continued growth and strategic investments.

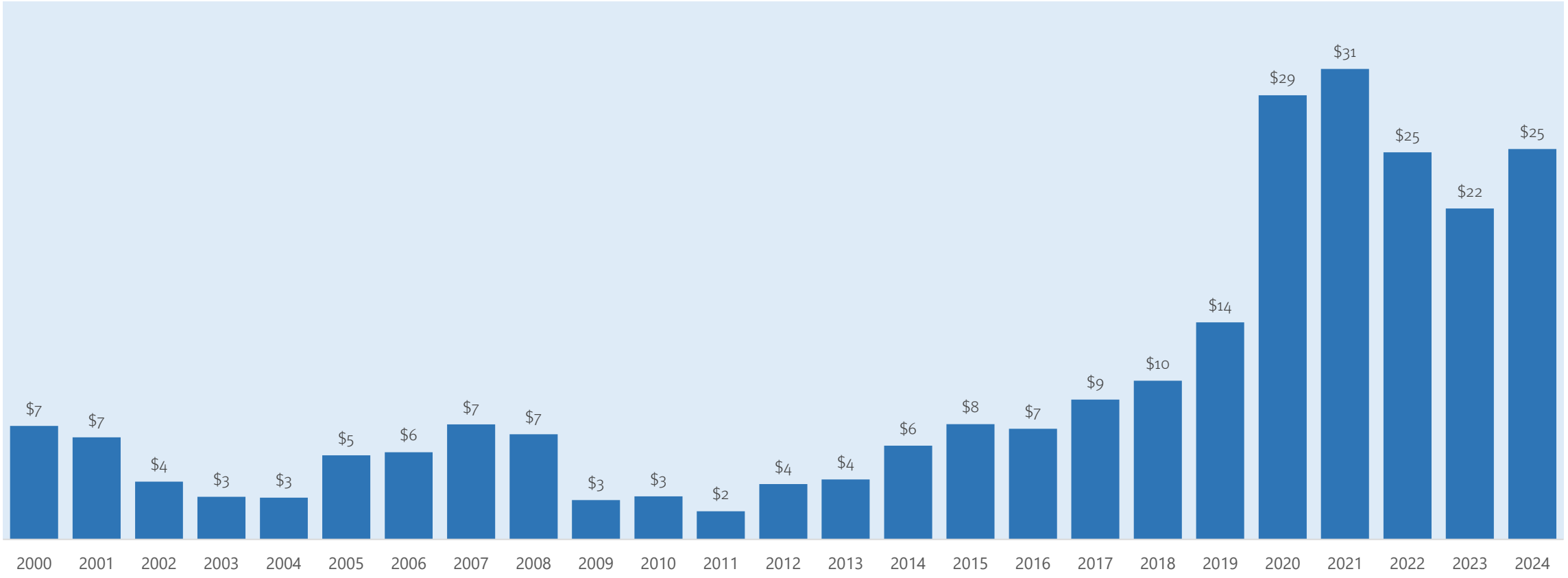
In addition, we previously entered into a commitment letter with certain holders of the Old Notes pursuant to which we expect to issue and sell to such holders in a private transaction additional New Notes in an aggregate principal amount of $131,450,000 (the "Concurrent Financing"). The proceeds from the Concurrent Financing will be used to repay the remaining amounts of Old Notes outstanding and to pay certain fees and expenses in connection with the Exchange Offer and the Concurrent Financing.

Source: https://www.prnewswire.com/news-releases/pl-developments-announces-fda-approval-for-omeprazole-otc-anda-and-successful-corporate-debt-refinancing-302289426.html

Venture Funds Raising Capital at a Strong Pace

This year is shaping up to be quite a strong year for venture fund capital formation. We are on pace to see $25 billion in announced raises. The actual amount raised is likely to be far higher as many funds are evergreen and don't announce new funds or just raise and keep quiet about it. The trend in recent years of the disappearance of smaller funds continues. This year's funding haul has been dominated by three groups that all raised three billion or more (Arch, Bain and Flagship). The market is becoming increasingly concentrated.

Biopharma Venture Capital Funds, Amounts Raise $mm, 2000 to 2024 (annualized)



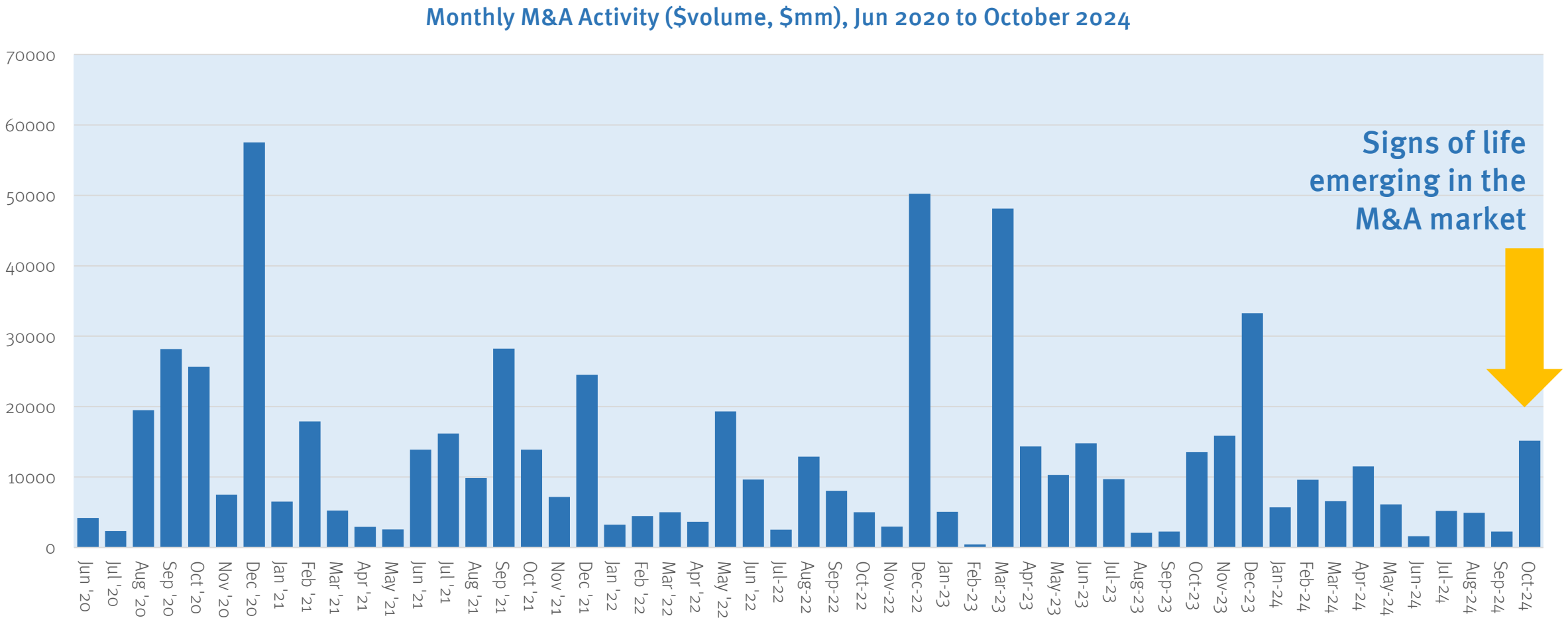
Source: Data from CapitalIQ, Crunchbase, Stifel research.

Deal News

Entry to a Top Chinese Venture Firm (https://lavfund.com/), October 2024

M&A Activity in October was the Strongest We Have Seen All Year

Led by Sanofi's $8bn OTC sale to CD&R and Lundbeck's buy of Longboard for $2.5 billion, we saw a robust M&A market emerge in October. Despite the strong month, the overall pace of M&A activity remains muted compared to any reasonable interval over the last decade.

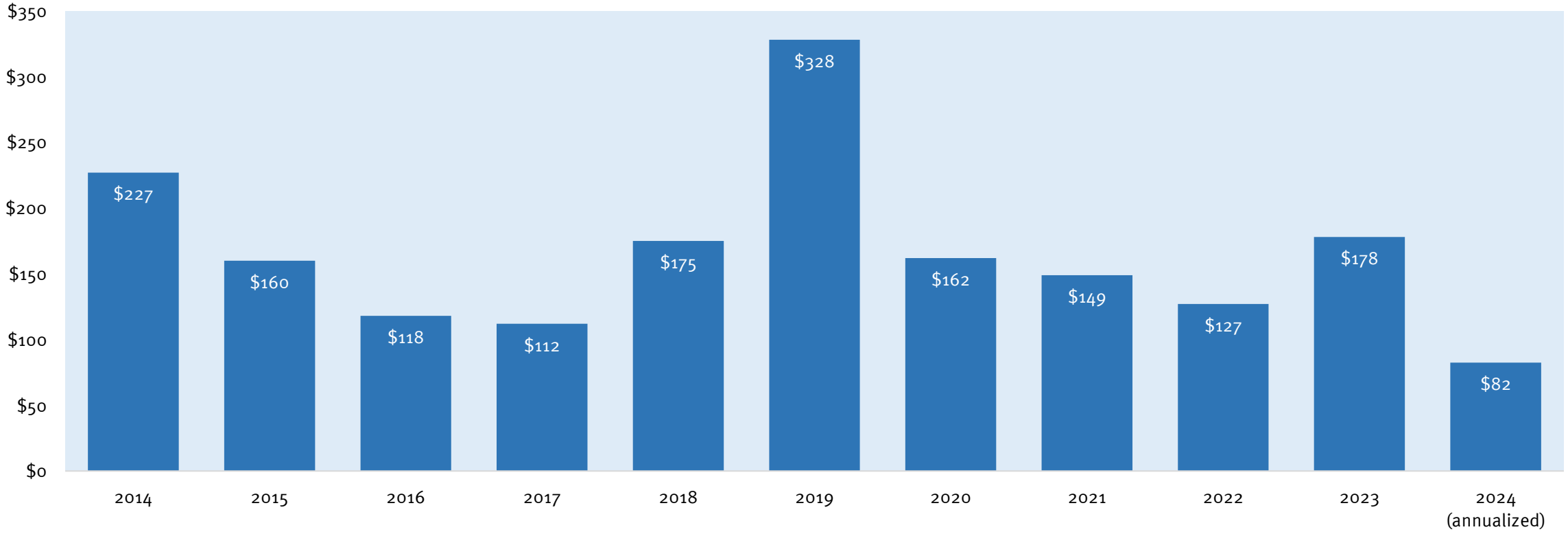


Source: S&P CapitalIQ

Data Through October 2024 Points to an Historically Quiet M&A Year

The strong October was not enough to save 2024 from a last place finish in M&A volume over the last decade. In contrast, China partnering has heated up in a big way.

M&A Volume in the Biopharma Sector, 2014 - 2024
($ Billions, Worldwide)



Source: Data from CapitalIQ, Stifel research.. M&A volume for 2024 was annualized as of October 31, 2024.

There Have Been *No* Biotech M&A Deals for More Than $5 Billion Upfront in 2024

Top Biotech / Spec Pharma M&A Deals, Jan 1 to Oct 30, 2024 (excluding OTC)

Announcement Date	Target	Buyer	Field	Stage of Lead Asset	Upfront Deal Value ($ millions)	Contingent Payments ($millions)
4/10/2024	Alpine Immune Sciences	Vertex Pharmaceuticals	Immunology	Phase II	4,900	0
2/12/2024	CymaBay Therapeutics	Gilead Sciences Inc.	Hepatology	Phase III	4,300	0
7/08/2024	Morphic Therapeutic	Eli Lilly and Co.	Immunology	Phase II	3,200	0
2/05/2024	MorphoSys AG	Novartis AG	Oncology	Approved	2,900	0
10/14/2024	Longboard Pharmaceuticals	H. Lundbeck A/S	Neurology	Phase III	2,600	0
4/29/2024	Deciphera Pharmaceuticals	Ono Pharmaceutical	Oncology	Approved	2,400	0
3/18/2024	Fusion Pharmaceuticals	AstraZeneca plc	Oncology	Phase II	2,000	400
1/08/2024	Ambrx Biopharma	Johnson & Johnson	Oncology	Phase II	2,000	0
4/03/2024	ProfoundBio Co.	Genmab A/S	Oncology	Phase II	1,800	0
1/23/2024	Inhibrx Inc.	Sanofi S.A.	Rare Disease	Phase II	1,700	500

Source: DealForma

Big Change: Seventeen Chinese Biotech Asset Deals with an Upfront Payments of $100 Million in 3 Years

Top China Outbound License Deals, Jan 1, 2022 to Oct 30, 2024

Date	Chinese Partner	Global In-Licensor	Asset	Deal Structure	Upfront Cash ($mm)	Total Deal Value ($mm)	Stage Signed
12/26/2023	Gracell Biotechnologies	AstraZeneca	CAR-t platform	Acquisition	$1,000	$1,200	Phase 1
9/30/2024	Regor Therapeutics	Roche	CDKx Platform	Asset Purchase	$850	NA	Phase 1
12/11/2023	Systimmune	BMS	EGFRxHER3 ADC	License	$800	$8,400	Phase 3
8/9/2024	Curon Biopharmaceutical	Merck	T-cell engager	Asset Purchase	$700	$1,300	Phase 1
12/5/2022	Akeso Biopharma	Summit Therapeutics	PD-1/VEGF bispecific	License	$500	$5,000	Phase 2
1/23/2023	Hutchmed	Takeda	VEGF inhibitor	License	$400	$1,130	Phase 3
10/28/2024	Chimagen	GSK	T-cell engager	Asset Purchsae	$300	$850	Phase 1
1/7/2024	Argo Bio	Novartis	RNA tx for CV	License	$185	$4,165	Phase 1
12/20/2023	Hansoh Pharma	GSK	B7-H3 ADC	License	$185	$1,710	Phase 2
11/9/2023	Eccogene	AstraZeneca	Oral GLP1 agonist	License	$185	$2,010	Phase 1
12/22/2022	Kelun-Biotech	Merck	ADC portfolio	License	$175	$9,513	IND Ready
10/30/2023	Hengrui Pharma	Merck KGaA	PARP1 inhibitor	License	$170	$1,487	Phase 1
4/3/2023	Duality Biologics	BioNTech	ADC portfolio	License	$170	$1,670	Phase 2
6/13/2024	Mingji Biopharm	AbbVie	TLA1 mAb	License	$150	$1,710	IND Ready
10/7/2024	CSPC Pharma	AstraZeneca	Oral LP(a) inhibitor	License	$100	$2,020	IND Ready
6/14/2024	Ascentage Pharma	Takeda	BCR-Abl Modulator	License Option	$100	$1,300	Phase 2
1/4/2022	3SBio	Syncromune Inc.	PD1 mAb	License	$100	$100	Phase 2

Source: DealForma and Stifel Research.

We Count 29 Biotechs Exploring "Strategic Options"

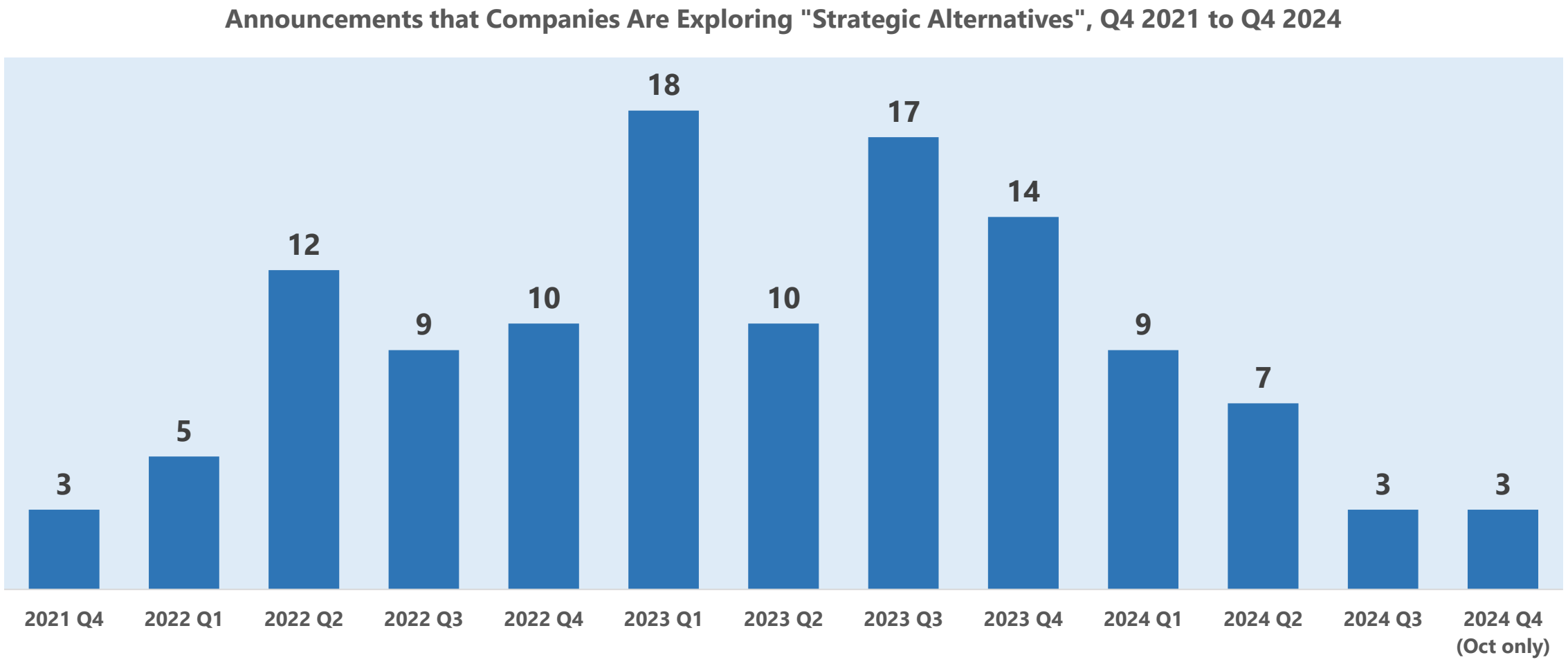
Date	Company	Cash ($mm)	EV ($mm)
11/1/2024	Essa	$131	-$62
10/22/2024	Marinus Pharma	$65	$49
10/1/2024	Gritstone	$50	$50
9/27/2024	Qualigen	$1	$4
6/28/2024	GeNeuro	$2	$17
7/22/2024	MEI Pharma	$38	-$18
7/11/2024	CARA Therapeutics	$70	-$43
5/28/2024	Ikena Oncology	$157	-$65
5/22/2024	Sonnet Bio	$4	$1
4/8/2024	Eyenovia	$8	$83
3/31/2024	Minerva	$31	$75
3/20/2024	Cyclacel	$3	$0
3/14/2024	Better Therapeutics	$7	$8
2/15/2024	Neurometrix	$16	-$10
1/8/2024	Pulmatrix	$12	-$4
1/4/2024	Portage Bio	$5	-$2
12/22/2023	Allovir	$141	-$31
12/7/2023	Hepion Pharmaceuticals	$19	-$4
10/30/2023	Zynex	$33	$343
8/29/2023	IRIDEX	$5	$32
8/14/2023	Alaunos Therapeutics	$4	$6
8/8/2023	Salarius Pharmaceuticals	$4	-$3
7/20/2023	Arcadia Biosciences	$9	-$3
6/30/2023	Spexis	$2	$11
6/24/2023	Bellorophon Therapeutics	$4	-$4
3/14/2023	Bellicum Therapeutics	$6	$0
2/8/2023	Genetether	$2	$1
9/26/2022	Exicure	$16	-$3
9/19/2024	Achilles Therapeutics	$95	$42

Source: Company press releases and Stifel research

The number of biotechs exploring strategic options is much reduced. We are seeing companies getting snapped up and fewer companies announcing that they have hit the point where it makes sense to explore options.

In recent weeks we have seen announcements by Aerovate and Glycomimetics to enter into merger deals that use their shells to allow private companies to go public

We are Seeing a Major Reduction in the Pace at Which Biotechs are Announcing the Exploration of Strategic Alternatives



Source: Company press releases and Stifel research

Industry News

Pfizer Earnings Show Signs of Turnaround

Ned Pagliarulo, *Biopharma Dive*, Oct 29, 2024 (excerpt)

Pfizer, facing down a contentious challenge from an activist investor, reported earnings for the third quarter Tuesday that handily beat Wall Street forecasts and led it to boost revenue guidance for the year.

Pfizer now expects to earn between $61 and $64 billion in 2024, up $1.5 billion at both ends of the range from its prior expectations. The pharmaceutical company also upped its estimate for adjusted diluted earnings per share by $0.30.

Sales between July and September totaled $17.7 billion, a growth of 32% year over year primarily driven by high demand for Pfizer's COVID-19 antiviral Paxlovid. But even excluding COVID products, sales rose by 14% compared to the third quarter of last year amid higher uptake for the company's rare disease drug Vyndaqel, prostate cancer treatment Xtandi and migraine medicine Nurtec ODT.

"Our performance through the first three quarters of the year is the result of our focus on our most important strategic priorities," Pfizer CEO Albert Bourla in a statement. "I'm confident that we will deliver on our financial commitments in 2024 and that we are well positioned to continue advancing scientific breakthroughs meaningful to our patients and our company, as well as creating long-term shareholder value, in the years to come."

This year and last, Pfizer moved to significantly cut costs as the global market for its COVID products, notwithstanding the current quarter, has shrunk overall. The restructuring has involved layoffs as well as changes to the company's operations and manufacturing.

Starboard claims that, under Bourla's leadership, Pfizer has destroyed tens of billions of dollars in market value by misfiring on expensive acquisitions and failing to deliver on research promises. In a recent presentation, the firm called for Pfizer's board to "hold management accountable," but didn't offer any specific proposals.

Source: https://www.biopharmadive.com/news/pfizer-third-quarter-beat-raise-paxlovid-starboard-challenge/731286/

Kymera Zeros in on Immunology, Seeks Partners for Cancer Candidates

Gabrielle Masson, *FierceBiotech*, Nov 1, 2024 (excerpt)

Kymera Therapeutics is pivoting focus from oncology to immunology, with plans to only develop cancer programs beyond phase 1 studies via partnerships.

The Watertown, Massachusetts-based biotech is making the switch based on “the significant progress and potential” of its immunology programs, which includes a midstage, Sanofi-partnered asset being tested in two indications.

“Focusing our resources and efforts on our work in immunology reflects our financial discipline around program prioritization to address large patient populations with significant need and clear substantial commercial opportunities,” Kymera's founder, president and CEO, Nello Mainolfi, Ph.D., said in an Oct. 31 release.

Source: https://www.fiercebiotech.com/biotech/kymera-zeros-immunology-seeks-partners-cancer-candidates

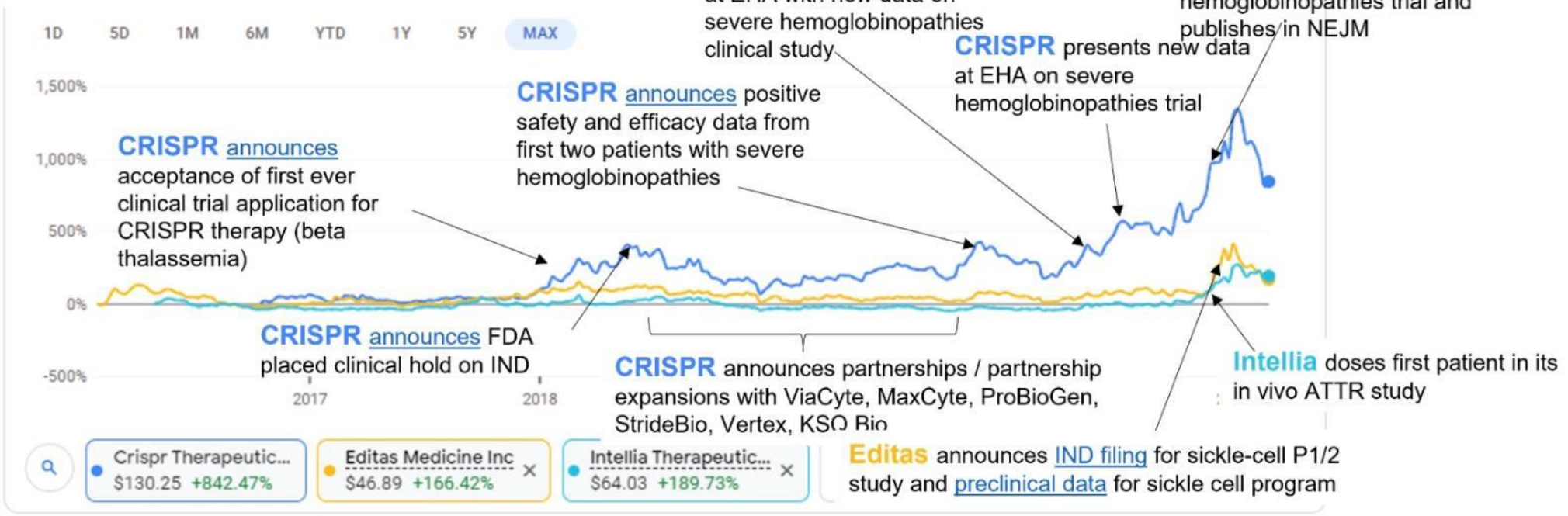
Bay Bridge Bio Analysis: Platform Companies Need to Generate Good Drugs to Perform in the Stock Market

Mkt cap at IPO

CRISPR: $551M
Editas: $571M
Intellia: $631M

Mkt cap at Mar-1-21

CRISPR: $9.8B
Intellia: $3.7B
Editas: $3.1B



Source: Bay Bridge Bio, Google finance, company press releases

Alpha Synuclein Blood-Based Biomarkers Could Accurately Diagnose Parkinson's Disease

Sunbird Bio Press Release, October 31, 2024

Sunbird Bio, a biotechnology company developing proprietary blood-based technologies to improve diagnosis and treatment of neurological disorders and early-stage cancer, announced new data demonstrating that the company's blood-biomarker alpha synuclein (α-synuclein) signatures accurately detect the aggregation of α-synuclein in the brain from a simple blood draw. Results from the study, which will be shared in a poster presentation (#116) on October 31 at the Clinical Trials on Alzheimer's Disease (CTAD) international conference, demonstrate that Sunbird's technology could provide blood-based diagnosis of multiple neurodegenerative diseases, including Parkinson's disease, with high accuracy.

Researchers in the Sunbird study prospectively collected blood samples from 16 individuals who were Parkinson's disease-positive, as well as from 24 age-matched healthy individuals. They then evaluated the ability of Sunbird Bio's proprietary α-synuclein assays to accurately distinguish between EV-bound and unbound soluble forms of α-synuclein in plasma.

Results suggest that a Sunbird-designed blood biomarker "control" signature composed of unbound soluble α-synuclein was unable to classify Parkinson's disease-positive samples, while the Sunbird Bio signature composed of brain-derived EV-bound α-synuclein accurately classified Parkinson's disease-positive samples with an area under the curve (AUC) of 0.86, indicating high accuracy in disease detection. These findings are not only applicable to the detection of Parkinson's disease, but also could have important implications in other neurological disorders, including Alzheimer's disease, that have common co-pathologies associated with α-synuclein aggregation.

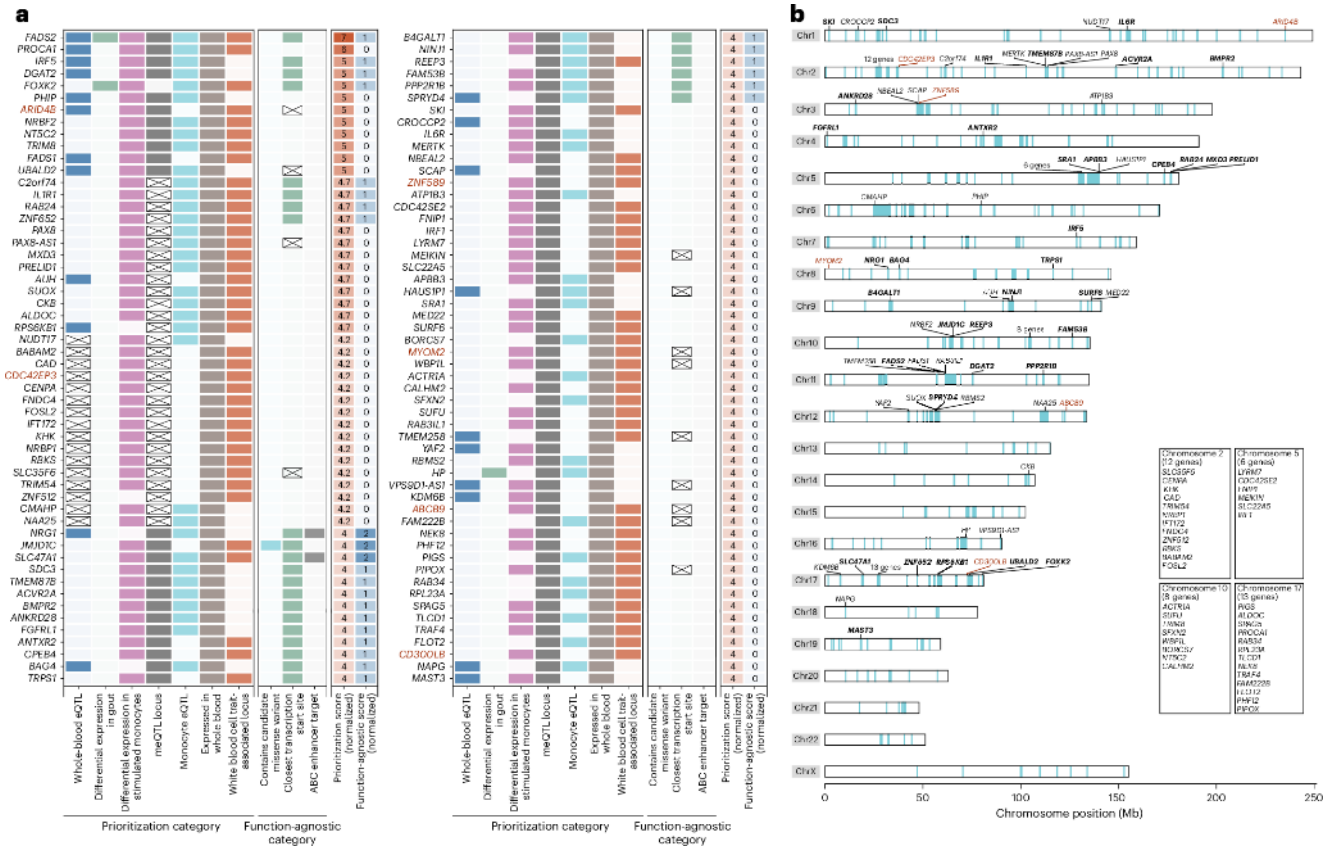
Source: https://www.businesswire.com/news/home/20241031668102/en/Sunbird-Bio-Presents-New-Clinical-Data-Demonstrating-Proprietary-Alpha-Synuclein-Blood-Based-Biomarkers-Could-Accurately-Diagnose-Parkinson%E2%80%99s-Disease

Gout Has a Major Genetic Component

Major, T.J., Takei, R., Matsuo, H. et al. A genome-wide association analysis reveals new pathogenic pathways in gout. *Nat Genetics*, October 15, 2024.

Gout is a chronic disease that is caused by an innate immune response to deposited monosodium urate crystals in the setting of hyperuricemia. Here, we provide insights into the molecular mechanism of the poorly understood inflammatory component of gout from a genome-wide association study (GWAS) of 2.6 million people, including 120,295 people with prevalent gout. We detected 377 loci and 410 genetically independent signals (149 previously unreported loci in urate and gout). An additional 65 loci with signals in urate (from a GWAS of 630,117 individuals) but not gout were identified. A prioritization scheme identified candidate genes in the inflammatory process of gout, including genes involved in epigenetic remodeling, cell osmolarity and regulation of NOD-like receptor protein 3 (NLRP3) inflammasome activity. Mendelian randomization analysis provided evidence for a causal role of clonal hematopoiesis of indeterminate potential in gout. Our study identifies candidate genes and molecular processes in the inflammatory pathogenesis of gout suitable for follow-up studies.

Genes prioritized for a role in gouty inflammation



a, One hundred eight genes with a normalized prioritization score ≥ 4 are ranked from highest to lowest score. The seven prioritization categories (left), three function-agnostic categories (middle) and the normalized scores (right) are given for each gene. Cells are colored if the gene gained a point in the prioritization and/or function-agnostic scores based on the criteria of that category and are crossed if category data were unavailable for that gene. Red gene labels represent those that were identified as a trans-eQTL. **b**, Ideogram showing the genomic location of the 108 genes with prioritization score ≥ 4. Bolded gene labels represent those that had a function-agnostic score ≥ 1, and red gene labels represent those that were identified as a trans-eQTL. Light blue highlighting within the ideogram chromosomes indicates the genomic location of all significant loci identified, amalgamated across all ancestry-specific, trans-ancestry and sex-specific analyses.

Source: https://www.nature.com/articles/s41588-024-01921-5

Study Busts Myths About Cause of Gout

University of Otago Press Release, Oct 15, 2024

A major international study has found gout is a chronic illness where genetics is a major cause, rather than lifestyle choices of the sufferer. Led by University of Otago researchers, the genome-wide association study, published in Nature Genetics, analysed the genetic information of 2.6 million people.

Researchers analysed amalgamated DNA data sets from around the world. About three quarters of the data was from customers of 23andMe, Inc, a direct-to-consumer genetics and preventative health company, who consented to participate in research. They found inherited genetics is an important part of why some people get gout and most others don't.

Senior author Professor Tony Merriman, of Otago's Department of Microbiology and Immunology, hopes the findings will remove some of the stigma around gout.

"Gout is a chronic disease with a genetic basis and is not the fault of the sufferer – the myth that gout is caused by lifestyle or diet needs to be busted.

"This widespread myth causes shame in people with gout, making some people more likely to suffer in silence and not go and see the doctor to get a preventive drug that lowers urate in the blood and will prevent their pain.

"People need to understand that while specific dietary factors, such as eating red meat, can trigger gout attacks, the fundamental cause is high urate levels, crystals in the joints, and an immune system primed to 'attack' the crystals – genetics plays an important role in all of these processes."

The research identified a large number of immune genes and immune pathways that provide new targets and approaches for preventing gout attacks.

Tony Merriman

Source https://www.nature.com/articles/s41588-024-01921-5

Obesity Market Update

Coming to work for patients, Indianapolis, 7am, August 2024

Eli Lilly's Q3 Miss for Tirzepatide Highlights Dependency on Wholesalers

Greg Slabodkin, *Biospace*, November 1, 2024 (excerpt)

Just when things were going well for Eli Lilly, it reported third-quarter earnings on Wednesday that were well below analysts' expectations. Sales of Lilly's type 2 diabetes drug Mounjaro and weight loss medication Zepbound—which share the same active ingredient, tirzepatide—both fell short of Wall Street forecasts. It was a rare quarterly miss for Lilly that prompted the company to lower its full-year 2024 guidance and sent the company's stock falling more than 13% in Wednesday morning trading.

The culprit behind Mounjaro and Zepbound's disappointing Q3 sales? "[I]nventory decreases in the wholesaler channel" following higher inventoried levels at the end of Q2, according to the company's earnings announcement. In a nutshell, Lilly blamed wholesaler destocking of its blockbuster drugs, which had been built up in previous quarters.

Anyone who has followed the red hot GLP-1 market is keenly aware of the volatile supply chain that Lilly and rival Novo Nordisk have tried to navigate, with both companies investing billions of dollars to ramp up their respective manufacturing capabilities in an attempt to keep up with unprecedented demand. Doses of both companies' GLP-1s wound up on the FDA's shortage list. The agency recently removed Mounjaro and Zepbound from the list but is currently rethinking that decision. Meanwhile, the FDA declared this week that all doses of Novo Nordisk's Ozempic and Wegovy are now available.

Lilly's Q3 results on Wednesday added a new wrinkle to the already challenging supply chain dynamics. Lilly CEO Dave Ricks in Wednesday's earnings call told analysts that the revenue miss for the GLP-1 drugs was not a function of supply but rather was due to wholesalers cutting down on their inventories. Lilly's wholesalers and retailers "are making their own decisions about which of the 12 different dosage forms they want to stock" and at what levels, Ricks said—something he conceded "we really don't control and don't attempt to."

While Ricks emphasized that U.S. demand for Mounjaro and Zepbound "has been strong and continues to grow as we expand both access and supply," Seigerman noted that building inventory will be key to a successful Q4. The problem, as Ricks explained on this week's call, is that Lilly is at the mercy of wholesaler stocking decisions.

Source: https://www.biospace.com/drug-delivery/eli-lillys-q3-miss-for-mounjaro-zepbound-highlights-dependency-on-wholesalers

Eli Lilly Has a Major Problem With Its Weight Loss Drugs Zepbound® and Mounjaro®

Victor Tangerman, *Futurism*, November 2, 2024 (excerpt)

Eli Lilly, the maker of the popular weight loss drug Zepbound, revealed what Bloomberg called a "shocking first miss" in its most recent quarterly sales announcement: in spite of bottomless hype, there just aren't enough people getting on its new weight loss drugs.

Shares plummeted by almost eight percent on Wednesday, with Zepbound and diabetes drug Mounjaro — the active ingredient in both is tirzepatide, a GLP-1 receptor agonist — missing Wall Street estimates by almost $900 million in sales.

That's despite the astronomical fanfare around weight loss drugs like Zepbound and its competitors, like Novo Nordisk's Ozempic and Wegovy. The drugs are a smashing success, both in terms of health outcomes and market penetration — but somehow that's not quite enough for the yawning expectations of capitalism.

Eli Lilly pointed the finger at inventory troubles, an excuse that didn't sit well with analysts.

In other words, could this be a sign that the seemingly insatiable demand for popular weight loss drugs could be starting to wane?

Unsurprisingly, Eli Lilly CFO Lucas Montarce tried to reassure investors, saying he didn't expect any more "big swings" in inventory going forward.

The company's competitors have been struggling with a similar problem. For instance, Novo Nordisk was forced to cut its annual profit expectations back in August following weaker-than-expected sales of its weight loss drugs Ozempic and Wegovy, which both use a different GLP-1 agonist drug called semaglutide.

Eli Lilly CEO Dave Ricks told investors during a call following the announcement that there wasn't a "demand problem here," but revealed that the company would start marketing Zepbound specifically directly to consumers, according to Bloomberg.

Meanwhile, supply shortages of weight-loss drugs like Zepbound and Ozempic have led to a surge in knockoff "compounder" drugs being sold, particularly online.

Naturally, Eli Lilly and Novo Nordisk have tried to discredit these companies, warning that their offerings contained impurities and were contaminated by bacteria.

Source: https://futurism.com/neoscope/eli-lilly-major-problem-weight-loss-drugs

Our View on What's Going on With Tirzepatide Sales

We agree with Lilly's comments that end market demand is there to drive tirzepatide much higher.

We have no visibility into end market demand and wholesaler stocking levels, but we would note that Lilly is doing a much better job of meeting demand with its supply given recent news on shortages nearing an end.

It stands to follow that wholesalers would rationally tend to hoard the medicine when it's in short supply and would stop holding high precautionary supplies when the supply improves.

As a result, we think that Lilly's story of a one-time wholesaler adjustment makes sense.

We also believe that poor reimbursement from commercial insurers is not helping matters. A fascinating poster at Obesity Week shows that when employers stop covering obesity medications, their employees shift to the less expensive compounded market and, also, tend to put on weight.

The pessimistic concern that Lilly's overall ability to grow this market may have hit a limit strikes us as completely unfounded based on a single quarter's results. We see this market showing high long-term growth as the incretin market for obesity drugs is less than 10% penetrated at this point.

Obesity Week Poster on What Happens When GLP-1 Coverage Ends

Impact of Loss of Employer-Sponsored GLP-1 RA Obesity Medication Coverage on Obesity Care

Deepali K. Ernest, MPH, PhD(c), Jackson M. Francis, MPH, Chellse L. Gazda, MD, MPH, Grant Herrington, MD, Marianne Olaniran, DrPH(c), MS, MPH, Luyu Xie, PharmD, PhD, M. Sunil Mathew, MS, Sarah E. Messiah, PhD, MPH, FTOS, Jaime P. Almandoz, MD, MBA, FTOS

Methods: This cross-sectional study analyzed self-reported data from an EHR-deployed survey among patients of an academic obesity medicine program who were employees of a large healthcare system that discontinued GLP-1RA obesity medicine coverage 6 months prior. Outcomes were evaluated by chi-square tests and logistic regression analysis
Results: The final analytical sample included 417 participants (mean age 51 years, mean body mass index 32.8 kg/m2, 91.07% female, 39.58% NHW, 27.98% NHB, 22.62% Hispanic, 9.82% Other ethnicity). The majority (84.5%) reported having difficulty managing their weight, and 30.62% were no longer on a GLP-1RA obesity medications. Those who stopped GLP-1RA obesity medications experienced greater weight recurrence (WR) of 4.92% total body weight compared to those still taking GLP-1RA, who regained 1.96% ($p<0.01$). Six-months post-loss of GLP-1 RA obesity medication coverage, 41% and 65.9% had <1 month supply of semaglutide and tirzepatide, respectively; 33.1% stockpiled medication, and 18.4% paid out of pocket (mean monthly expense $402) for GLP-1RA medications. **To prolong supply, 29.9% reduced doses, 27.3% switched to non-GLP-1RA obesity medications, 1.3% sought bariatric surgery, and 3.9% abandoned their weight loss journey. Alarmingly, 55.1% were unaware of FDA guidance against using compounded GLP-1RA, while 5% bought and 40.2% considered buying compounded GLP-1RA medications for weight loss.** Participants currently not taking obesity medications were 4% more likely to have WR(%) (OR=1.04, CI: 1.01-1.08, $p<0.01$) vs. those taking obesity medications
Conclusions: Results here show loss of GLP-1RA obesity medication coverage has negative impacts on obesity care with a greater odds of weight recurrence and high prevalence of desires to pursue non-evidence-based therapies like compounded GLP-1RA weight loss medications. Additional research, policy and education are needed to optimize access to evidence-based obesity care

Source: https://tos.planion.com/Web.User/AbstractDet?ACCOUNT=TOS&ABSID=1124975&CONF=OW2024&ssoOverride=OFF&CKEY=564OX3122

Exposure to Sugar Rationing in the First 1000 Days of Life Protected Against Chronic Disease

Tadeja Gracner et.al, *Science*, October 31, 2024

We examined the impact of sugar exposure within 1000 days since conception on diabetes and hypertension, leveraging quasi-experimental variation from the end of the United Kingdom's sugar rationing in September 1953. Rationing restricted sugar intake to levels within current dietary guidelines, yet consumption nearly doubled immediately post-rationing. Using an event study design with UK Biobank data comparing adults conceived just before or after rationing ended, we found that early-life rationing reduced diabetes and hypertension risk by about 35% and 20%, respectively, and delayed disease onset by 4 and 2 years. Protection was evident with in-utero exposure and increased with postnatal sugar restriction, especially after six months when solid foods likely began. In-utero sugar rationing alone accounted for about one third of the risk reduction.

In our obesity report from July 2024 we argued that one important explanation for obesity that could be addressed with a "one and done" approach was sugar addiction. There is strong evidence that sugar consumption creates an addiction phenotype. This most recent paper provides the strongest evidence yet for this theory.

What's so intriguing is that we are making great progress in the development of drugs that reduce addictive behavior.

It's worth noting that use of GLP-1's appears to reduce addictions overall. This is the converse argument but one that is consistent with brain chemistry and addiction driving obesity and other addictive behaviors.

Source: https://www.science.org/doi/10.1126/science.adn5421

Can Zapping the Brain Help Treat Addiction?

Julie Wernau, *Wall Street Journal*, October 29, 2024 (excerpt)

MORGANTOWN, W.Va.—Joe Hilton was inside an MRI machine, wearing a $1 million helmet and goggles showing him pictures of heroin being cooked in a spoon and injected into an arm.

Doctors behind a glass partition used the MRI images to ensure ultrasound waves from the helmet were correctly aimed at a target in Hilton's brain a couple of millimeters in size. Then, more than 1,000 probes pulsed ultrasound waves to this area, known as the brain's reward center. After the treatment Hilton, 39 years old, tried to mentally connect with the pictures of a drug he had used for more than two decades. Instead of causing him to sweat and shake with cravings as he had minutes earlier, the pictures felt meaningless. Inside the MRI machine, he pressed a button on a joystick to let the doctors know his cravings had dropped to near zero.

"It just wasn't there, the feeling," he said later in a hospital room.

In Appalachia, in the heart of one of the earliest and deadliest waves of the opioid crisis, doctors at West Virginia University's Rockefeller Neuroscience Institute are conducting a radical experiment. Using focused ultrasound waves, they are resetting cells inside the brain's reward center, the nucleus accumbens. They hope the procedure can treat addictions ranging from drugs like opioids and methamphetamine to gambling and eating.

Source: https://www.wsj.com/health/healthcare/addiction-treatment-ultrasound-brain-stimulation-58d6dec3

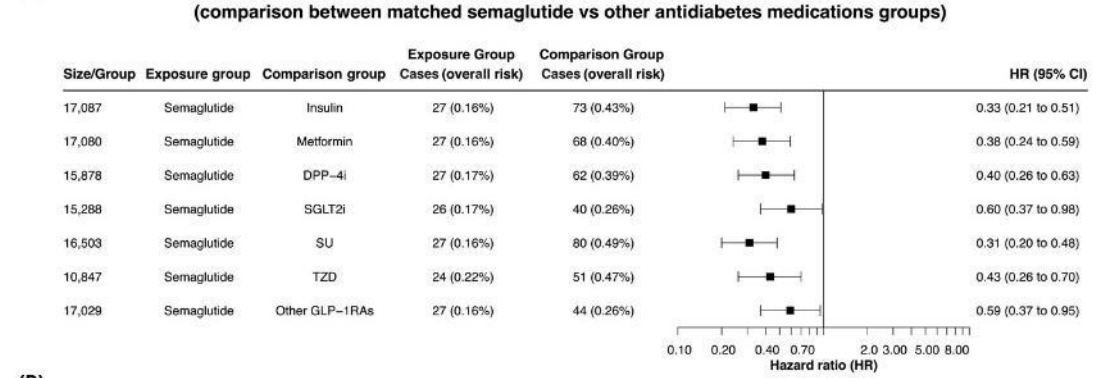
Associations of Semaglutide with First-Time Diagnosis of Alzheimer's Disease in Patients with Type 2 Diabetes

Wang, William et.al, *Alzheimers and Dementia*, October 24, 2024

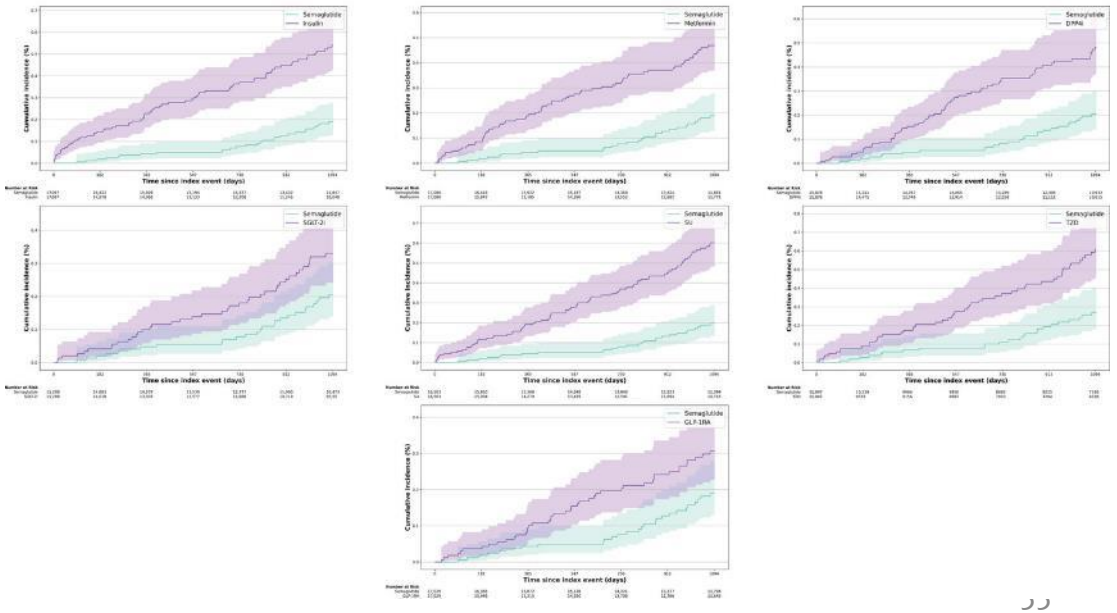
In our study of real-world populations with T2DM, a high-risk group for AD, semaglutide showed a lower risk of first-time AD diagnosis or AD-related medication prescriptions compared to insulin, other non-insulin/non-GLP-1RAs, and other GLP-1RAs. These results were similar for older patients, both genders, and those with and without obesity. Cumulative incidence curves began to diverge within 30 days and continued to separate thereafter, indicating semaglutide's potential to delay or slow AD development with sustained effects. Our large-scale study of 1,094,761 US patients with T2DM found semaglutide associated with a 40% to 70% decrease in first-time AD diagnoses, including a 40% reduction compared to other GLP-1RAs. Ongoing randomized trials are assessing semaglutide's therapeutic effects in early AD. Our findings support conducting future prevention trials to determine semaglutide's ability to delay or slow down the onset of AD.

(A) Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure Group Cases (overall risk)	Comparison Group Cases (overall risk)	HR (95% CI)
17,087	Semaglutide	Insulin	27 (0.16%)	73 (0.43%)	0.33 (0.21 to 0.51)
17,080	Semaglutide	Metformin	27 (0.16%)	68 (0.40%)	0.38 (0.24 to 0.59)
15,878	Semaglutide	DPP–4i	27 (0.17%)	62 (0.39%)	0.40 (0.26 to 0.63)
15,288	Semaglutide	SGLT2i	26 (0.17%)	40 (0.26%)	0.60 (0.37 to 0.98)
16,503	Semaglutide	SU	27 (0.16%)	80 (0.49%)	0.31 (0.20 to 0.48)
10,847	Semaglutide	TZD	24 (0.22%)	51 (0.47%)	0.43 (0.26 to 0.70)
17,029	Semaglutide	Other GLP–1RAs	27 (0.16%)	44 (0.26%)	0.59 (0.37 to 0.95)



(B)



Source: https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.14313

Pfizer Highlights GDF-15 Based Weight Gain Medication for Cancer Cacheixia Patients Last Week

Pfizer Pflash: A Spotlight on

Cancer Cachexia and

Ponsegromab

an investigational monoclonal antibody targeting growth differentiation factor-15 (GDF-15)

Pfizer Research & Development

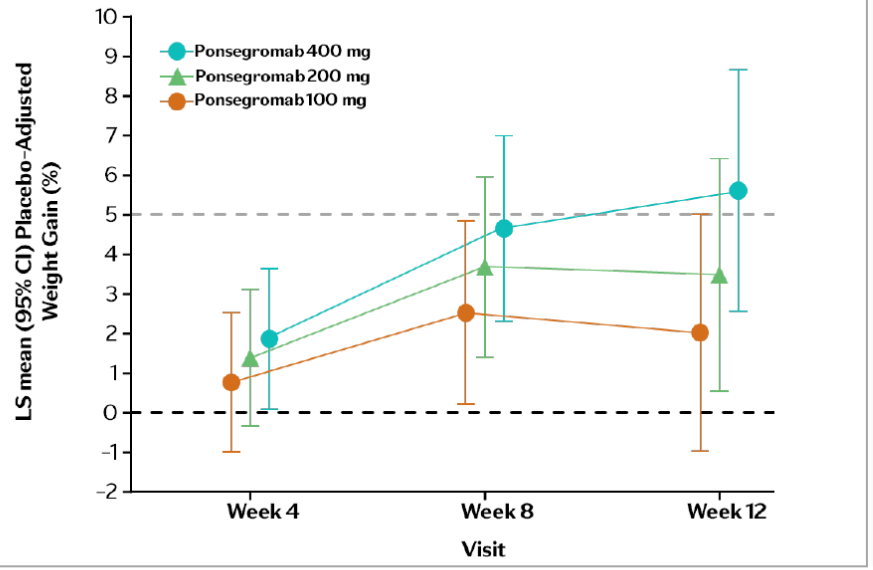
We think this could be a very meaningful drug for Pfizer because the market is so big and the need large. The market is huge and the notion that cancer patients could *gain* weight is unheard of.

Interestingly, on the next page we show a fresh abstract from Cincor's GDF-15 analogue (opposite of ponsegromab). It results in nice weight loss – something that we hadn't seen with previous GDF-15 analogues (the quantum at eight weeks is eerily similar and points to basis physiology). It's starting to look like GDF-15 is an important axis for weight management in general.

Primary Endpoint Met: Dose-Dependent Weight Gain with Ponsegromab

Ponsegromab was generally considered safe & well tolerated with increases in body weight at all doses tested in Ph 2

Placebo-Adjusted Weight Gain Exceeds 5% in 400 mg Dose Group at 12 Weeks[1]



Weight Gain >5% Suggested by Cancer Cachexia Endpoints Working Group as Being Clinically Meaningful[2]

Pfizer Research & Development

1. Crawford et al. European Society for Medical Oncology Congress 2024. 2. Brown LR et al. J Cachexia Sarcopenia Muscle 2024; 15: 816-52.
Ph: Phase; LS: Least squares; CI: Confidence interval

9

Source: https://investors.pfizer.com/files/doc_events/2024/Nov/01/Pfizer-Pflash_A-Spotlight-on-Cancer-Cachexia-and-Ponsegromab_FINAL.pdf

Obesity Week: Cincor's GDF-15 Analogue Achieves 3.7% Weight Loss at Eight Weeks

Effect of CIN-109, a Novel GDF-15 Analog, on Body Weight and Composition in Subjects With Obesity

Mary H. Bond, MS, MBA, Brian Murphy, MD, MPH, FIDSA, Satya Shreenivas, MD, MBA, Mackenzie Pater, PhD, MBA, Brendan Doran, PharmD, Jon Isaacsohn, MD

Background: CIN 109 is a novel HSA GDF15 fusion protein with a long half-life (12-14 days) being developed for weight management.
Methods: This was a Phase 1 randomized, double-blind, placebo-controlled, multiple ascending dose study assessing the safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of CIN-109. Otherwise healthy subjects with obesity were randomized to receive placebo or CIN-109 subcutaneously once weekly (at doses of 5 mg, 10 mg, 15 mg, 20 mg, or 40 mg) or once every other week (QOW; at doses of 20 mg, 40 mg, or 60 mg). The weekly groups were treated for 4 weeks and the biweekly groups for 8 weeks. Safety assessments included clinical laboratory tests, vital signs, physical examinations, 12-lead ECGs, and adverse events. Blood samples to characterize the PK and immunogenicity of CIN-109 and for exploratory biomarkers were collected. PD measures included 24-hour food intake, body weight, and body composition (using DEXA).
Results: A total of 68 subjects were randomized in a 3:1 active:placebo ratio; 59 subjects completed the study. Mean weight and BMI of CIN-109-treated subjects were ~100 kg and ~35 mg/m^2, respectively.
There were no treatment-related serious adverse events (AEs). Moderate nausea and moderate emesis each occurred in 16.7% of the subjects. A total of 2 subjects discontinued due to GI AEs after the first dose. QOW dosing was associated with fewer, less severe GI AEs as compared to weekly dosing.
CIN-109 exposures increased in a generally dose proportional manner and weekly dosing was associated with greater accumulation than QOW dosing.
Generally dose-dependent decreases in food intake up to ~50% and decreases in body weight up to ~3.7% were observed within 1-2 months of dosing with CIN-109. The highest QOW dose was associated with a decrease in fat mass and an increase in lean mass.
Conclusions: CIN-109 was well-tolerated and produced meaningful decreases in weight. At the highest dose tested, the vast majority of the weight loss was from a reduction in fat mass

Obesity Week: Cincor's PYY Analogue Shows Meaningful Weight Loss after Just One Week of Dosing

Safety, Pharmacokinetics, and Effect of Novel PYY Analog CIN-110 on Weight in Subjects With Obesity

Mary H. Bond, MS, MBA, Satya Shreenivas, MD, MBA, Brian S. Murphy, MB, MPH, FIDSA, Mackenzie Pater, PhD, MBA, Brendan Doran, PharmD, Jon Isaacsohn, MD

Background: CIN-110 is a novel long-acting PYY_{3-36} analog being developed for weight management. CIN-110 is designed to gradually increase then sustain drug exposures following subcutaneous (SC) dosing to avoid GI side effects observed with rapid increases in PYY.
Methods: This was a Phase 1 randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of CIN-110. Otherwise healthy subjects with obesity were randomized in a 3:1 active:placebo ratio.
Safety assessments included clinical laboratory tests, vital signs, physical exams, 12-lead ECGs, and adverse events (AEs). Blood samples to assess PK were collected. PD measures included 24-hour food intake and body weight.
Results: A total of 24 subjects are included in this interim data review (6 active and 2 matching placebo subjects for each of the following CIN-110 doses: 0.5 mg, 1.5 mg, and 4 mg). Mean baseline weight and BMI of each group were ~102 kg and ~34 kg/m², respectively.
There were no serious AEs or AEs leading to withdrawal. All AEs were mild or moderate. All moderate events were non GI-related. In total, 3 mild events of nausea were reported with no increase in incidence with increasing dose. Nausea events typically occurred within 12-48 hours postdose and resolved within ~24 hours while exposures to CIN-110 were still near peak.
PK results demonstrate that CIN-110 exposures increase gradually. Peak concentrations typically occurred within 2-3 days after dosing and were sustained with an ~14-day half-life.
Caloric intake and body weight decreased with CIN-110 as compared to placebo. **Decreases in food intake and body weight of up to ~21% and ~1.8%, respectively, were observed within 1 week after dosing.**
Conclusions: CIN-110 was well-tolerated and produced noteworthy decreases in caloric intake and weight as compared to placebo after a single subcutaneous dose. CIN-110's design features and resulting PK and safety profiles make it a promising candidate for further development treat obesity.

Obesity Week: Safety, Tolerability, and Clinical Effects of Zealand's Petrelintide (ZP8396), A Long-acting Amylin Analog

Minna Braendholt Olsen, PhD, Zealand Pharma A/S, Jonathan Griffin, PhD, Ulrike Hoevelman, MD, Stanislava Macura, Thue Johansen, MD, PhD, Berith Fredsted Hagen, Helle Frimer-Larsen, Evan Frary, Dan Hesse, Tim Heise, MD

Background: Petrelintide is a novel amylin analog designed for once weekly subcutaneous administration in development for weight management. Previous tolerability and safety data, as well as body weight reductions, observed with single and multiple dosing even without dose escalation encouraged further investigations.

Methods: This randomized, double-blind, placebo-controlled, 16-week treatment, phase 1b trial assessed safety, pharmacokinetics, and pharmacodynamics of once weekly subcutaneous petrelintide in healthy participants with BMI 27-39.9 kg/m2. Forty-eight participants (79% male, median age: 49 years, median BMI: 29 kg/m2, median body weight: 92 kg) were randomized (3:1) within three dose cohorts. Dose escalation was used to reach different maintenance doses, administered for twelve, eight and six weeks, respectively.

Results: Based on an interim data cut after participants completed 16 weeks of dosing, petrelintide was well tolerated, with no serious or severe adverse events (AEs). All gastrointestinal AEs were mild, except for two moderate events (nausea and vomiting) reported in one participant who discontinued treatment; there were no other treatment discontinuations due to AEs. No other events of vomiting occurred and there were two events of diarrhea, both mild. **Nausea was reported in 16.7-33.3% for petrelintide, vs. 16.7% for placebo.**
After 16 weeks, mean body weight reductions were 4.8%, 8.6% and 8.3%, for the three petrelintide treated groups, respectively, versus 1.7% for the pooled placebo.

Conclusions: Treatment with petrelintide appeared safe, was well tolerated, and resulted in clinically meaningful body weight reductions of up to 8.6% after 16 weeks. Gastrointestinal adverse events were mostly mild, transient in nature and occurred during dose escalation. This underlines the potential of petrelintide as an anti-obesity treatment, with efficacy comparable to GLP-1 receptor agonists but with better tolerability. The efficacy and safety of petrelintide will be further investigated in a phase 2 trial.

Obesity Week: Viking VK2735 Oral Looks Good in Overweight Adults

First-in-Human Study of an Oral Formulation of the GLP-1/GIP Co-Agonist VK2735 in Healthy Adults

Joel Neutel, MD, FASH, FACC, Orange County Research Center, Angela Rowland, Francesca Bell, Carmela T. Rooney, Chris Rask, Becky Steele, Summer Ji, Geoff Barker, PhD, Marianne Mancini, MA, MBA, Brian Lian, PhD

Background: Concomitant activation of the glucose-dependent insulinotropic polypeptide polypeptide (GIP) receptors has been shown to potentiate the satiety and insulin-sensitizing effects of glucagon-like peptide 1 (GLP-1) receptor activation, leading to enhanced clinical benefits relative to GLP-1 activation alone. VK2735 is a peptide agonist of the GLP-1 and GIP receptors that has demonstrated promising safety, tolerability, and weight loss effects in obese subjects treated up to 13 weeks using weekly subcutaneous dosing. A tablet formulation of this compound was evaluated in healthy adults.

Methods: This trial was a randomized, double-blind, placebo-controlled Phase 1 study in healthy adults with BMI ≥30 kg/m^2. The primary objective of the study was to evaluate the safety and tolerability of VK2735 administered as an oral tablet once daily for 28 days. Exploratory measures evaluated changes in body weight and other metrics.

Results: Oral VK2735 demonstrated encouraging safety and tolerability following 28 days of once-daily dosing at doses up to 40 mg per day. Among subjects receiving VK2735, all treatment emergent adverse events were reported as mild or moderate, with the majority (76%) reported as mild. Gastrointestinal (GI) adverse events were also reported as mild or moderate (79% mild). Vomiting was not reported among VK2735-treated subjects at doses up to 40 mg/day; diarrhea was reported in one subject (3%) receiving VK2735 compared with two (20%) receiving placebo. **Overall, no clinically meaningful differences were reported for GI-related adverse events among subjects treated with VK2735 compared with placebo.** Cohorts receiving VK2735 dosed at up to 40 mg/day demonstrated **dose-dependent reductions in body weight from baseline, ranging up to 5.3%.** Cohorts receiving VK2735 dosed at up to 40 mg/day also demonstrated reductions in mean body weight relative to placebo. Based on the preliminary data, dose escalation above 40 mg/day was pursued. Data from all completed cohorts will be presented.

Conclusions: A oral tablet formulation of the peptide GLP-1/GIP agonist VK2735 demonstrated encouraging signs of weight loss with a benign safety and tolerability profile following 28 days of once-daily dosing in healthy obese volunteers. Further evaluation of the tablet formulation in a Phase 2 trial is planned.

Obesity Week: Viking VK2735 Injectable Delivers in Overweight Adults

Results From the 13-Week VENTURE Phase 2a Study of the GLP-1/GIP Co-Agonist VK2735 in Obese Subjects

Joel Neutel, MD, FASH, FACC, Orange County Research Center, Naim Alkhouri, MD, FAASLD, DABOM, Harold E. Bays, MD, MFOMA, FTOS, FACC, FNLA, FASPC, DABOM, Sureka Bollepalli, MD, Kelly Bowman, MD, Parke Hedges, MD, FACOG, John Pullman, MD, FACP, Gary Reiss, MD, MBA, Summer Ji, Geoff Barker, PhD, Scott C. Stubbe, Marianne Mancini, MA, MBA, Brian Lian, PhD

Background: Co-activation of the glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors has been shown to decrease glucose, reduce appetite, lower body weight, and improve insulin sensitivity in patients with type 2 diabetes, obesity, or both. VK2735 is a dual agonist of the GLP-1/GIP receptors that has demonstrated encouraging safety, tolerability, and signs of clinical activity in a prior 4-week clinical study in healthy volunteers with a BMI ≥30 kg/m^2. A Phase 2a trial was conducted to evaluate longer-term treatment in adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related comorbidity.
Methods: The Phase 2 VENTURE trial was a randomized, double-blind, placebo-controlled study intended to evaluate the safety, tolerability, pharmacokinetics, and weight loss efficacy of VK2735, administered subcutaneously, once weekly for 13 weeks in 176 adults who are obese (BMI ≥30 kg/m^2), or adults who are overweight (BMI ≥27 kg/m^2) with at least one weight-related comorbid condition. The primary endpoint of the study was the assessment of the percent change in body weight from baseline to Week 13 among patients treated with VK2735 as compared with placebo, while secondary and exploratory endpoints evaluated a range of additional safety and efficacy measures.
Results: VK2735 demonstrated encouraging safety and tolerability following 13 weeks of once-weekly dosing. Among patients receiving VK2735, the majority (92%) reported drug related treatment emergent adverse events as mild or moderate in severity. **The majority of TEAEs that were gastrointestinal (GI) in nature (95%) were also reported as mild or moderate.** GI-related adverse events were generally observed early in treatment, with decreasing frequency upon repeat dosing. **Patients receiving VK2735 demonstrated statistically significant reductions in mean body weight after 13 weeks, ranging up to 14.7% from baseline**. Reductions in body weight were progressive through the course of the study, with no plateau observed.

Obesity Week: AZ's Amylin Receptor Agonist Shows Similar AE Profile to Zealand Drug (No Weight Loss Data Yet)

Safety, Tolerability, and Pharmacokinetics of AZD6234, a Long-Acting Agonist of the Amylin Receptor

Mitra Rauschecker, MD, Senior Medical Director, Astra Zeneca, Elin R. Carlsson, Simina Boca, Johanna Melin, PhD, Xiao Tu, PharmD, Sami Omar

Background: Despite currently available weight loss treatments, a significant proportion of patients do not tolerate therapeutic dose titrations and thus do not reach desired weight loss goals, so alternative therapies are needed. AZD6234 is a potent agonist of amylin receptors with selectivity over calcitonin receptor activity. We assessed the safety, tolerability, and pharmacokinetics (PK) of AZD6234 in a phase 1 first-in-human study in healthy participants with overweight or obesity.

Methods: This randomized, single-blind, placebo-controlled SAD study evaluated s.c. administration of 0.3 mg, 0.9 mg, 1.5 mg, 2.7 mg, 3.0 mg, and 4.2 mg. Intravenous and s.c. administration in a Japanese cohort were also evaluated, at doses of 0.3 mg i.v. and 2.7 mg s.c., respectively. Participants were randomized 6:2 to AZD6234 or placebo. Primary outcomes included safety and tolerability, secondary outcomes included pharmacokinetics.

Results: Overall, 54 participants (46 male, 8 female) were included in the study, (median age 42.5 years, mean BMI 28.8 kg/m^2). There were no deaths or other serious adverse events. In the global cohorts, adverse events (AEs) were more common in the pooled AZD6234 group than in the placebo group (approximately 57.1% and 9.1%, respectively). In the i.v. and Japanese s.c. cohorts, AEs were reported by 3 (50.0%) and 4 (80.0%) participants, respectively. The most common AEs were nausea, decreased appetite, and vomiting. Exposure was approximately linear from 0.9 mg to 4.2 mg and peak drug concentration occurred between 8 and 36 hours post-dose. A statistically significant decrease in body weight compared to placebo was observed in s.c. cohorts, from the lowest dose of 0.3 mg, with no significant changes in the i.v. cohort.

Conclusions: AZD6234 was generally well tolerated with no major safety concerns at doses up to 4.2 mg in healthy participants. The full data will be presented at the Obesity Week meeting in November 2024.

Obesity Week: Structure's GSBR-1290 Saw 6 to 7% Weight Loss at 12 Weeks with Manageable Side Effects

Significant and Clinically Relevant Weight Changes at 12 Weeks With Small Molecule GLP-1RA,GSBR-1290

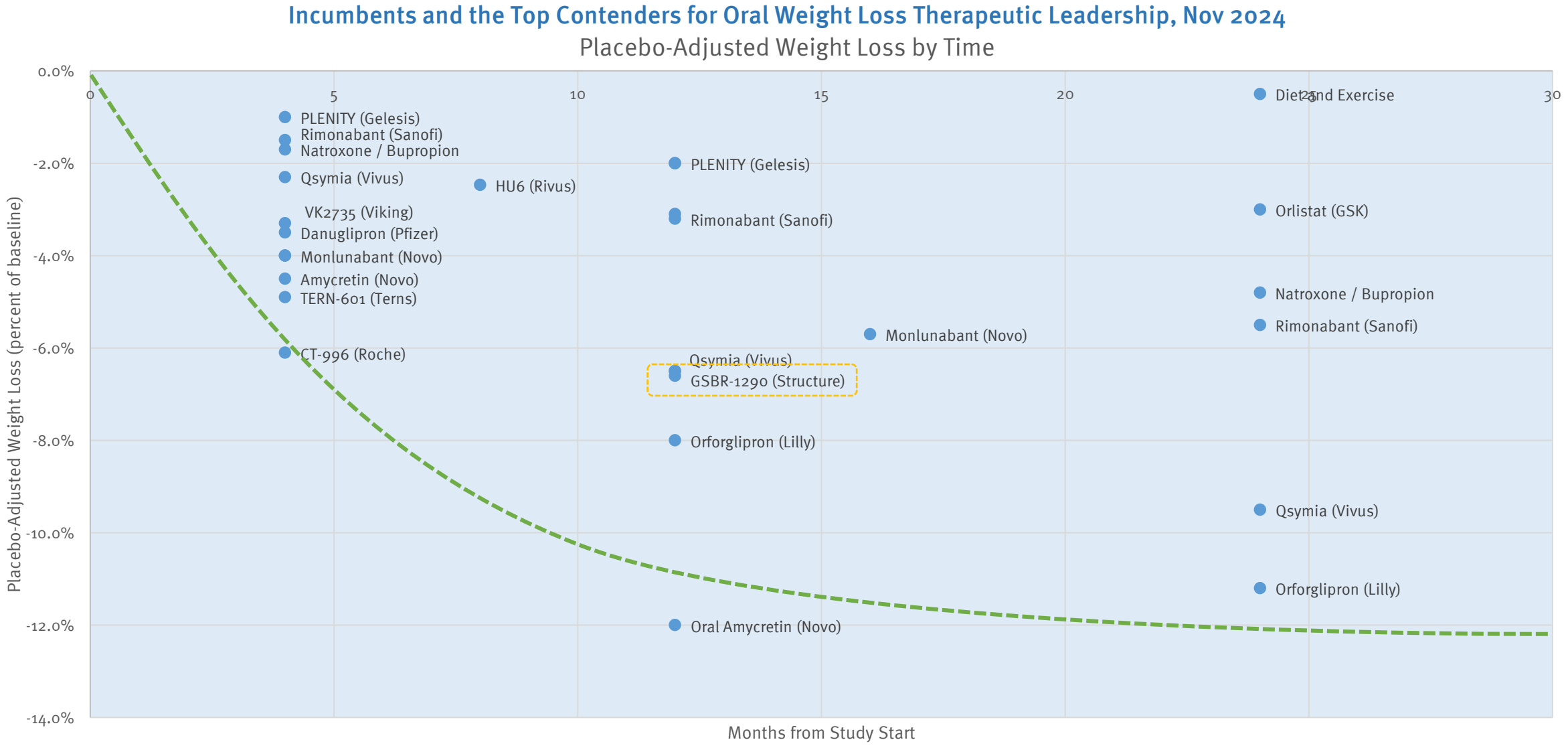
Leo Seman, Executive Director, Clinical Development, Structure Therapeutics Inc., Huibin Yue, PhD, Ke Liu, PhD, Aline Barth, Divya Chari, Michael Pelayo, Blai Coll, Mark A. Bach, MD, PhD

Background: Several injectable peptide GLP-1RAs are approved for chronic weight management (CWM) but accessibility remains a challenge globally. GSBR-1290 is a novel, oral, non-peptide GLP-1RA in development for CWM, as a potential alternative to injectable peptides. These studies were designed to evaluate the safety, tolerability, and efficacy of GSBR-1290 in overweight or obese participants.

Methods: The safety, tolerability, and effects on body weight (BW) of daily (QD) GSBR-1290 were investigated in 2 studies. Both studies aimed for 12 weeks of exposure with 60 or 120mg/QD as target doses. Study 1 (N=64 randomized 3:1 to GSBR-1290 or placebo) followed a weekly titration scheme, starting at 5mg up to 120mg. Study 2 (N=54 randomized in 3 cohorts) followed differing titration schemes (1, 2 or 4 week) to assess the impact on tolerability.

Results: Baseline characteristics for Study 1 were 62% male, mean age 44 years, and BMI 31.6 kg/m^2. Study 2 enrolled equal number of males/females, mean age 47 years, and BMI 29 kg/m^2. **Both studies showed significant BW reduction in those receiving GSBR-1290, ranging from 6.2-6.9% placebo-adjusted (P<0.0001), with the majority achieving at least a 5% BW reduction at 12 weeks. Study discontinuations due to adverse events (AEs) ranged from 5.4%-11.1%; the most common AEs were gastrointestinal (GI). The frequency of GI events attenuated over time despite increasing doses of GSBR-1290.** There were no events of drug induced liver injury. GSBR-1290 showed generally dose-proportional exposure between 60-120mg and the plasma concentration of GBSR-1290 remained above 10 ng/mL[1] for 24 hours at 120mg QD.

Oral Weight Loss Leadership Curve as of Nov 4, 2024



company announcement

Semaglutide 2.4 mg demonstrates superior improvement in both liver fibrosis and MASH resolution in the ESSENCE trial

Bagsværd, Denmark, 1 November 2024 – Novo Nordisk today announced the headline results from part 1 of the ongoing ESSENCE trial, a pivotal phase 3, 240-week, double-blinded trial in 1,200 adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate to advanced liver fibrosis (stage 2 or 3)[1]. Part 1 of the ESSENCE trial evaluated the effect of once-weekly semaglutide 2.4 mg on liver tissue (histology) compared to placebo on top of standard of care for the first 800 randomised people at 72 weeks.

The trial achieved its primary endpoints by demonstrating a statistically significant and superior improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis with semaglutide 2.4 mg compared to placebo. At week 72, 37.0% of people treated with semaglutide 2.4 mg achieved improvement in liver fibrosis with no worsening of steatohepatitis compared to 22.5% on placebo[2]. 62.9% of people treated with semaglutide 2.4 mg achieved resolution of steatohepatitis[3] with no worsening of liver fibrosis compared to 34.1% on placebo[2].

In the trial, semaglutide 2.4 mg appeared to have a safe and well-tolerated profile in line with previous semaglutide 2.4 mg trials.

"We are very pleased about the ESSENCE clinical trial results and the potential of semaglutide to help people living with MASH" said Martin Holst Lange, executive vice president and head of Development at Novo Nordisk. "Among people with overweight or obesity, one in three live with MASH. This has a serious impact on their health and represents a significant unmet need."

Novo Nordisk expects to file for regulatory approvals in the US and EU in the first half of 2025. The detailed results from ESSENCE will be presented at a scientific conference in 2024. Part 2 of the ESSENCE trial will continue with expected readout in 2029.

Semaglutide 2.4 mg demonstrates superior improvement in both liver fibrosis and MASH resolution in the ESSENCE trial. Fibrosis improvement at 72 weeks was modest, but statistically significant (37% versus 22.5% with placebo). MASH resolution was 63% versus 34% on placebo.

Source: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=171971

Madrigal, 89Bio Jump after Novo's Semaglutide Shows Promise in MASH

The Fly, *Yahoo Finance*, November 2, 2024

Shares of companies developing therapies for the liver disease metabolic steatohepatitis, or MASH, are rallying after Novo Nordisk (NVO) said its GLP-1 drug semaglutide showed "superior improvement" in treating the disease in a trial. Novo Nordisk announced the headline results from part 1 of the ongoing ESSENCE trial, a pivotal phase 3, 240-week, double-blinded trial in 1,200 adults with metabolic dysfunction-associated steatohepatitis, or MASH, and moderate to advanced liver fibrosis. Part 1 of the ESSENCE trial evaluated the effect of once-weekly semaglutide 2.4 mg on liver tissue compared to placebo on top of standard of care for the first 800 randomized people at 72 weeks. The trial achieved its primary endpoints by demonstrating a statistically significant and superior improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis with semaglutide 2.4 mg compared to placebo. "We are very pleased about the ESSENCE clinical trial results and the potential of semaglutide to help people living with MASH. Among people with overweight or obesity, one in three live with MASH. This has a serious impact on their health and represents a significant unmet need," said Martin Holst Lange, executive vice president and head of Development at Novo Nordisk. Madrigal Pharmaceuticals (MDGL), which recently got approval for its drug Rezdiffra, is up $57.73, or 22%, to $317.07 while shares of other companies working in the space – 89Bio (ETNB) and Akero Therapeutics (AKRO) – have risen 16% and 1%, respectively.

So what's going on here? Why would Novo competitors rise in value after Novo releases positive data on semaglutide in NASH?

The answer is clear enough. The data from semaglutide was not competitive with what is achievable with Madrigal's REZDIFFRA® and 89Bio's FGF21 drug.

Source: https://finance.yahoo.com/news/madrigal-89bio-jump-novo-semaglutide-160054758.html

Disclosure

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