Biopharmaceutical Sector

Update – Nov 18, 2024

STIFEL | Healthcare

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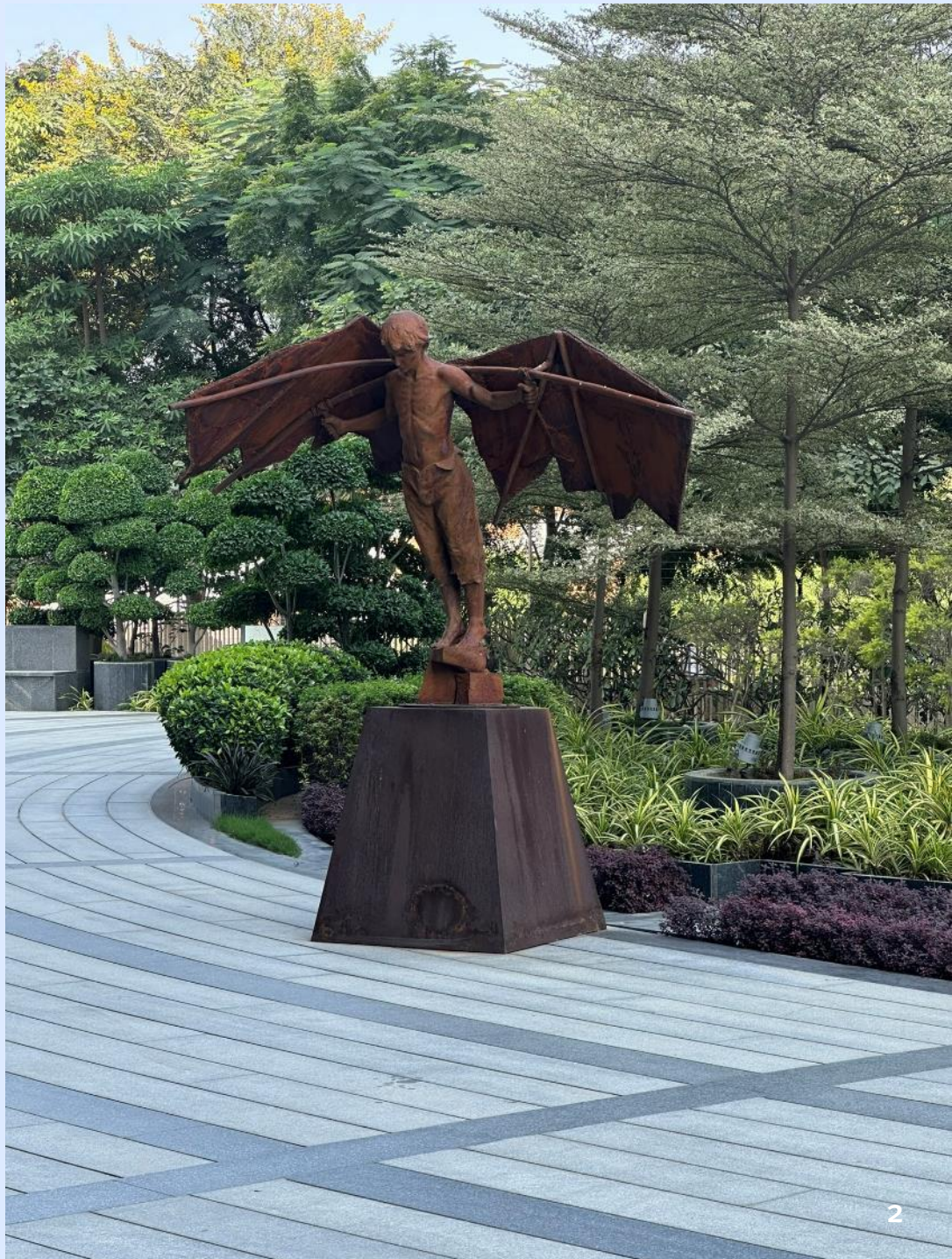

Statue designed to inspire innovation at the Entrance to Zydus Lifesciences Headquarters, Ahmedabad, India, November 2024

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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A pitch for life sciences in Sweden seen at Bio-Europe, Stockholm, November 2024

Join Us at These Upcoming Events

Biotech Hangout held its latest event on November 15th.

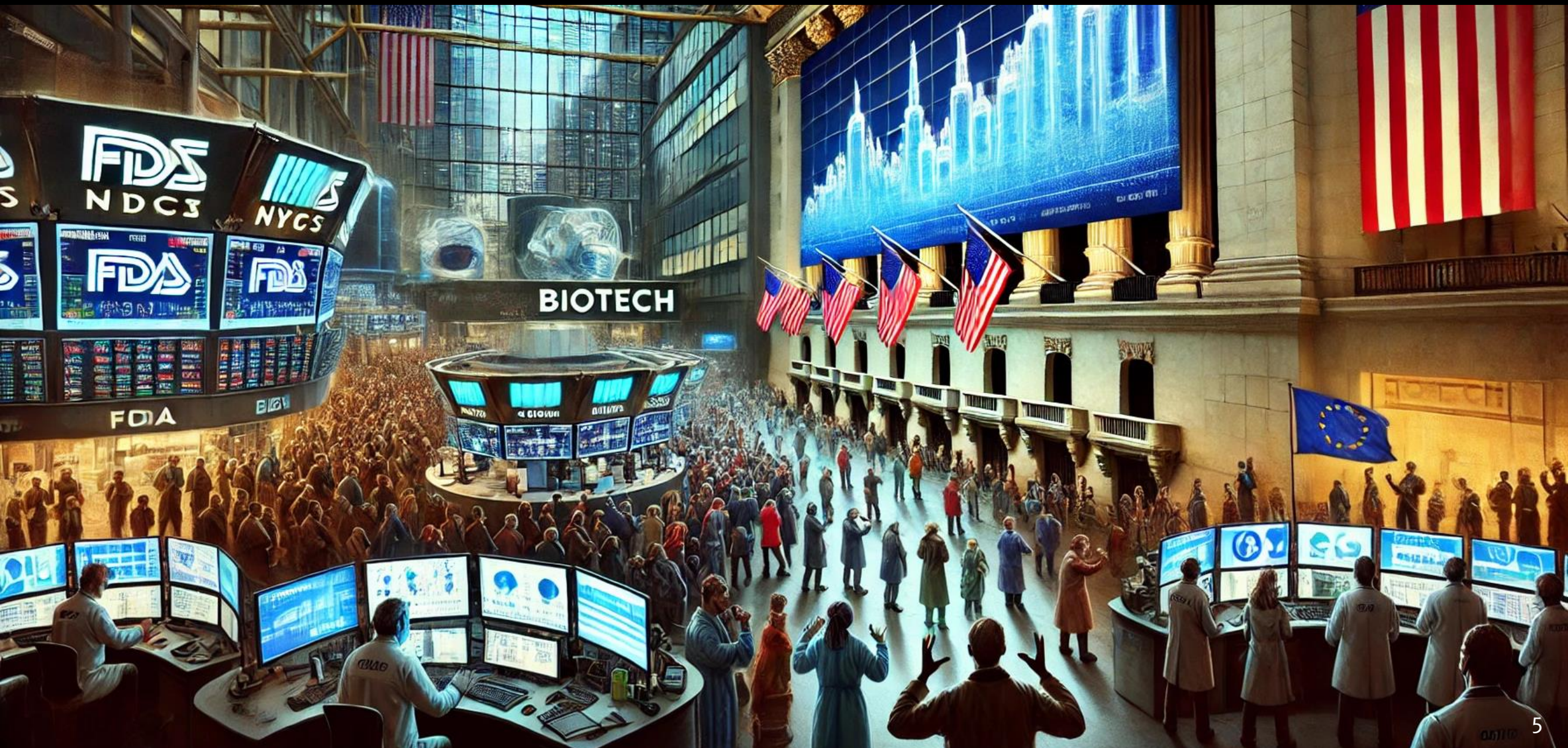
Please join us next Friday at noon EST for the latest episode.

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

The week of Jan 13, 2025 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 13th.

To meet with Stifel
yeungn@stifel.com

The U.S. Political Situation and Bioinnovation



XBI Down Big on Trump's Appointment of RJK Jr. to HHS Role

Hopes for a centrist and constructive set of healthcare policies from the Trump administration were dashed last week after the message that RFK Jr. is to be appointed to the job of HHS Secretary.

RFK Junior himself has indicated a desire to use his new role to combat chronic disease stating on his web account:

> "Thank you @realDonaldTrump for your leadership and courage. I'm committed to advancing your vision to Make America Healthy Again. We have a generational opportunity to bring together the greatest minds in science, medicine, industry, and government to put an end to the chronic disease epidemic. I look forward to working with the more than 80,000 employees at HHS to free the agencies from the smothering cloud of corporate capture so they can pursue their mission to make Americans once again the healthiest people on Earth."

Despite these positive words, the biopharma market went into freefall on the news. The XBI dropped from 104 to less than 92 at Friday's close.

It was as if RFK Jr. indicated he was planning to double down on the IRA and drug price controls.

We spoke to a number of industry observers and heavy hitters after the news hit and can share the broad industry view on RFK, Jr. It's not positive.

Industry Negative on RFK Jr.

One well-known long-serving former large pharma CEO said it simply: “he’s not fit for office.”

The view was that the man is not experienced in administration, attaches himself to unorthodox views – all the while espousing an interest in health and evidence-based approaches.

There are a number of reasons to worry about the overall set up:

1. RFK Jr. can drive out a lot of the individuals who have been driving good decisions at both HHS and FDA.
2. It is likely that Trump’s new colleagues focused on “government efficiency” (Elon Musk and Vivek Ramaswamy) will take an interest in health policy and spend and work with RFK Jr. to shrink high value institutions that will report to RJK Jr. like FDA, CDC and NIH.
3. RFK’s stated interests including vaccine policy, sugared cereals and water fluoridation are not aligned with the interests of industry and could derail well-intended efforts of government and industry to advance healthcare innovation.
4. RFK Jr. has been negative on the CDC and public health infrastructure. This is not good.

One can also come up with arguments to be positive on RFK Jr’s appointment and to indicate that HHS and FDA will likely be positive for industry.

Cause for Hope

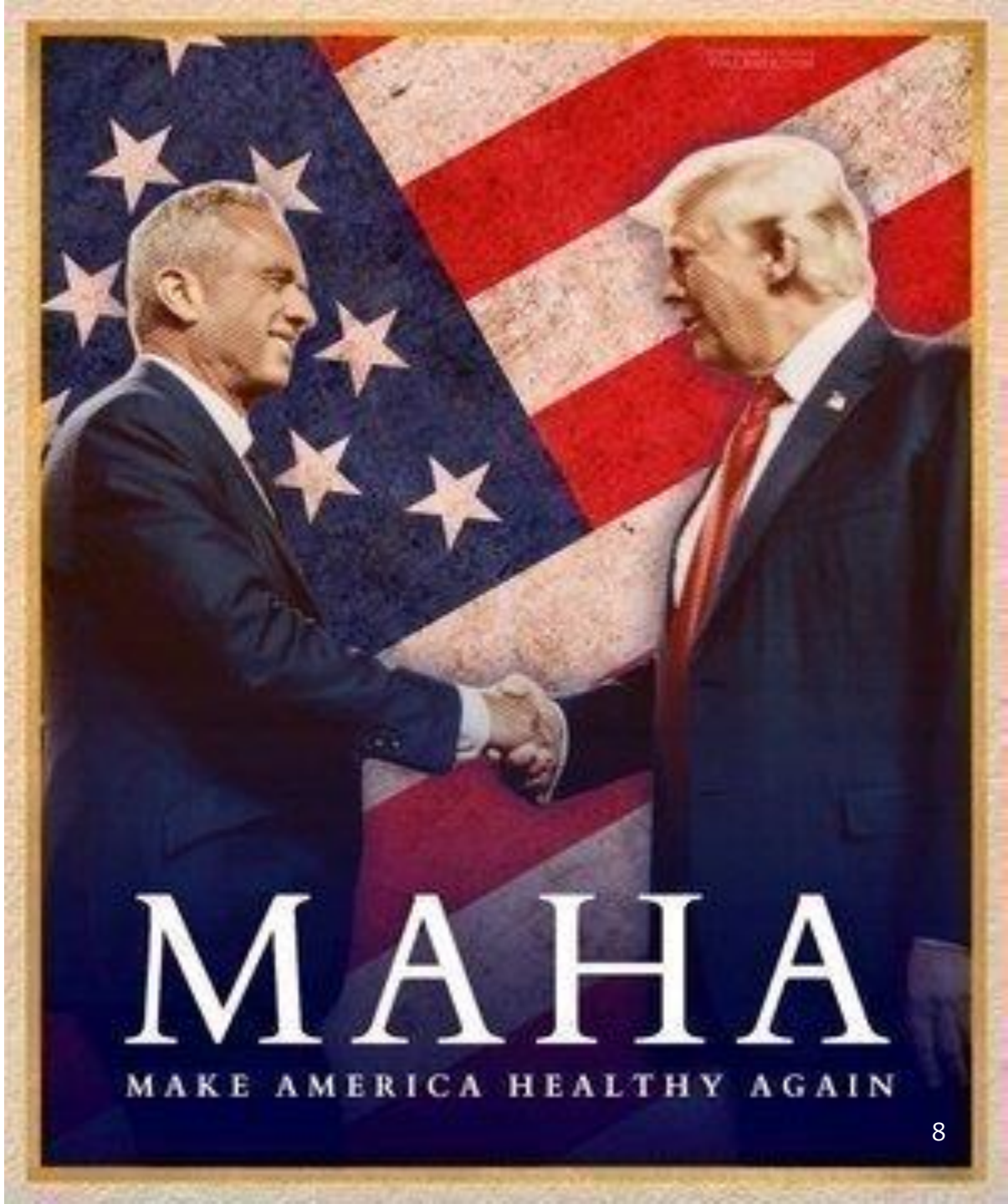
These arguments include:

1. There is a long-standing need for improved food labelling. RFK Jr. last week highlighted the overconsumption of highly processed foods as a priority for him.
2. RFK Jr. has proposed banning the provision of highly processed foods in schools. This is very likely a good idea.
3. There is little legal mechanism to do things like take fluoride out of the U.S. water system. This is not an area of federal purview.
4. Even vaccine regulation is not as easily changed as one might think. The CDC makes recommendations about vaccine use but has little statutory authority to mandate use of vaccines or to prohibit their use.

The ultimate reason not to worry about RFK Jr. is that he may not actually get the HHS job if he is not confirmed by the Seanate.

The reasoning we have heard from knowledgeable sources indicates that he is not as aligned with Trump as one might think. Our sources suggest that Trump had pushed RFK Jr. to take on a White House “Health Czar” role while RFK Jr. wanted the HHS position. Trump apparently relented but this may have been quite the Machiavellian move as he now faces a brutal Senate confirmation process.

Industry has considerable sway in Senatorial decisions and RFK Jr.’s overall poor reputation is such that even with a Republican majority in the Senate, he could easily go down in a nomination fight.



Does RFK Jr. Make it Through the Senate?

An article by Daniel Payne in *Politico* last Friday noted that many Republican senators come from states that would be threatened by populist stances on food policy.

Mr Payne wrote: “Companies would prefer to let their allies in the Senate, buttressed by years of campaign contributions and revolving-door hires, sideline Kennedy before they spend political capital to fight him.”

To get through the Senate, RFK Jr.’s nomination has to get through the Senate Finance Committee where is support among Republicans is tepid at best (see https://www.politico.com/live-updates/2024/11/15/congress/robert-f-kennedy-jr-hhs-confirmation-00189833).

Further, many of RFK Jr.’s policy ideas would likely face successful legal challenges (see https://www.politico.com/news/2024/10/31/trump-rfk-food-pharma-00186513).

Interestingly, while RFK Jr. is not a *friend* of pharma he is also not an obvious foe.

He is indeed not a fan of the FDA but it does not follow necessarily that proposed changes at FDA would be negative for industry.

Our own view is that RFK Jr’s proposed appointment has some chance to survive the Senate and, further, is not likely to be a net positive for pharma.

The potential positive impacts of the Trump election on the IRA and M&A policy are still likely to materialize and our own view is that the negative reaction to the RFK Jr. appointment is overdone. His negative effects on industry, if any, are ultimately likely to be modest.

Robert F. Kennedy Jr.’s Billion-Dollar Hit to Big Pharma

DealBook, *New York Times Reuters*, Nov 15, 2024 (excerpt)

That didn’t take long. Shares in big vaccine producers, including Pfizer and Moderna, tumbled soon after Donald Trump named Robert F. Kennedy Jr. as his choice to lead the Department of Health and Human Services.

Picking Kennedy, long a polarizing figure in the worlds of public health and food policy, underscored the president-elect’s desire to disrupt Washington with highly unconventional cabinet picks. Whether Kennedy — or Matt Gaetz, Pete Hegseth or Tulsi Gabbard, for that matter — can get Senate confirmation is another question.

The choice suggests that Trump wants to drastically overhaul U.S. public health policy. Kennedy’s divisive views — including skepticism about vaccines, pesticides and water fluoridation — are well known. (As is his sowing of misinformation.) But he has now been picked to lead a huge department with 80,000 employees, whose regulations affect America’s food and medicine choices.

Kennedy provided crucial political support for Trump during the campaign, so it seemed likely that he would get significant influence. Trump is seeking to give him real power to, in the president-elect’s words, help “ensure that everybody will be protected from harmful chemicals, pollutants, pesticides, pharmaceutical products, and food additives.”

Though he’s perhaps best known for his vaccine skepticism, Kennedy last week told NPR that “we’re not going to take vaccines away from anybody.”

That hasn’t reassured investors in vaccine makers, who lost more than $8 billion in market value on Thursday. Shares in Pfizer fell 2 percent; Moderna 5.6 percent; and BioNTech and Novavax by 7 percent.

Source: https://www.nytimes.com/2024/11/15/business/dealbook/trump-robert-f-kennedy-stocks.html

Trump Nominee RFK Vowed to Purge the FDA. It Won't Be So Easy

Ahmed Aboulenein and Michael Erman, *Reuters*, Nov 15, 2024

Kennedy has been most vocal about the FDA, an agency that oversees nearly $3 trillion in medicines, food and tobacco products. In interviews and on social media, Kennedy has accused agency staff of doing the bidding of Big Pharma and Big Food. "FDA's war on public health is about to end," Kennedy wrote on X in late October. "If you work for the FDA and are part of this corrupt system, I have two messages for you: 1. Preserve your records, and 2. Pack your bags." FDA officials were not immediately available to comment on the Kennedy nomination.

Shares of vaccine makers including Pfizer Inc, and Moderna, fell after news of Kennedy's appointment and were down in after-hours trading by as much as 2%. Del Bigtree, who was director of communications for Kennedy's election campaign and remains close to the former candidate, said he expected a careful look at any FDA employee ties to industry. "You're going to see a vetting process of, how do the people have the jobs here? What were their conflicts of interest . . . you're going to watch a transparency that should have happened," he said. "And it's all going to be made public."

Making good on such pledges would require the new Trump administration to strip federal employees of protections against arbitrary firing put in place by lawmakers. The 18,000 FDA staff are further shielded because their salaries are not exclusively funded by Congress. In 2024, $3.3 billion, almost 46% of the agency's $7.2 billion budget, came from so-called "user fees," or payments made by pharmaceutical and medical device manufacturers to fund the staff resources needed to review their products quickly, conduct inspections, and ensure the safety of clinical trials. The FDA says user fees do not influence its decisions to approve products, and its overall budget is still subject to Congressional approval. Congress renews the user fee program every five years and most recently extended its use through September 2027.

Others were more blunt about their concerns about Kennedy's long-held views.

"Putting somebody in charge of any public health service who is a vaccine denier puts at risk the stability of the nation at large," Jeremy Levin, CEO of biotech company Ovid Therapeutics and a former chairman of biotech lobby group BIO told Reuters late last month. "Vaccine denialism, which is a central plank of RFK's, is perhaps as dangerous as anything as you could imagine." Levin described previous Trump appointees at the FDA and a project overseeing the successful development of COVID-19 vaccines during his first term as "exceptional choices." "We have to hold on to the hope that anybody who gets put into the position of the FDA director in a Trump administration would be of the same quality," he said. In the meantime, FDA Commissioner Robert Califf sought to reassure staff members following Trump's election last week. "There will, no doubt, be changes ahead, but rest assured, the FDA will continue to do the job it was created to do," he wrote in an email viewed by Reuters. "The work you do will remain critical and this agency will continue to protect the public, as it has for over a century."

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/rfk-jr-vow-purge-fda-sets-up-collision-with-big-pharma-2024-11-15/

The Flouride Factor

Trump says RFK Jr.'s proposal to remove fluoride from public water 'sounds OK to me'

By Aaron Pellish, CNN

Updated 3:21 PM EST, Sun November 3, 2024

01:35 - Source: CNN

Pollster explains how some RFK Jr. policies highlight a growing political shift

Despite the above comments, there is overwhelming evidence supporting the use of flouride in the water supply. See:

1.Centers for Disease Control and Prevention. Achievements in Public Health, 1900-1999: Fluoridation of Drinking Water to Prevent Dental Caries. *JAMA*. 2000;283(10):1283–1286. doi:10.1001/jama.283.6.735

2.U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries. *Public Health Rep.* 2015;130(4):318–331. doi: 10.1177/003335491513000408

3.Griffin SO, Regnier E, Griffin PM, Huntley VN. Effectiveness of fluoride in preventing caries in adults. *J Dent Res*. 2007;86(5):410–414.

4.Water fluoridation for the prevention of dental caries. *Cochrane Database of Syst Rev*. 2015;(6). Art. No.: CD010856. doi: 10.1002/14651858.CD010856.pub2.

5.O'Connell JM, Rockell J, Ouellet J, Tomar SL, Maas W. Costs and savings associated with community water fluoridation in the United States. *Health Aff*. 2016.35(12):2224–2232. doi: 10.1377/hlthaff.2016.0881

Flouride Facts

Water flouridation levels are kept in the U.S. to between 0.7mg / L and 1mg/L.*

The evidence linking fluoride (F-) to bone fracture risk indicates that, if anything, this level of fluoride in the water *reduces* the risk of bone fractures.

However, RFK Jr. is right to note that *theoretically*, high levels of fluoride in the water could increase fracture risk. However, the U.S. is *nowhere near* those levels of fluoridation. See, for example:

Fluoride exposure and risk of fractures: a systematic review and dose-response meta-analysis

I Iamandii ✉, R Mazzoli, L De Pasquale, M Vinceti, T Filippini

European Journal of Public Health, Volume 34, Issue Supplement_3, November 2024, ckae144.1420, https://doi.org/10.1093/eurpub/ckae144.1420

Published: 28 October 2024

The evidence linking fluoride use to neurodevelopment disorders, cancer and thyroid disease largely comes out of China where there can be abnormally high amounts of fluoride in the groundwater due to natural factors. However, there is *no evidence* that we could find, linking fluoride use at levels found in the U.S. water supply to these disorders.

A recent peer-reviewed write-up of the situation by Ping Zhao et.al. (2023) summarized as follows:
"F– is one of the most essential trace elements for human growth, and an appropriate amount of F– is conducive to preventing dental caries and promoting bone growth (Sarinana-Ruiz, et al., 2017; Gao et al., 2020; Li et al., 2020). Both insufficient and excessive F– cause great harm to human health. Specifically, a lack of F– tends to cause dental caries, and excessive intake leads to fluorosis (Katsanou et al., 2013; Tarki et al., 2020; Nafouanti et al., 2021; Senarathne et al., 2021). The common diseases caused by excessive F– intake are dental fluorosis and skeletal fluorosis, which may lead to death in severe cases (Xie et al., 1999; Mondal et al., 2016; Mohammadi et al., 2017; Liu et al., 2021). F– can cause biochemical effects, such as acute poisoning (vomiting, hemoptysis, hand and leg spasm, cardiac arrest, etc.), long-term chronic poisoning (gene mutation, allergic diseases, Alzheimer's disease, etc.), and carcinogenic and mutagenic effects, mainly due to the effect of fluorination (Liu et al., 2015a; Patil et al., 2018; Kurdi 2016; Nikiforova 1982; Maitra et al., 2021; Morales-Arredondo et al., 2016). All F– is toxic. Acute fluorosis results when the daily intake of F– is higher than 4 mg, and its toxicity is higher than that of lead and lower than that of arsenic. Long-term F– accumulates in human teeth and bones under a high-fluoride environment, which can damage human soft tissue and intellectual development and even lead to an increased risk of tumors and leukemia (Mumtaz et al., 2015; Durrani and Farooqi, 2021; Senthilkumar et al., 2021). According to the latest reports, long-term, excessive intake of F– has also been linked to adverse cancer and distortion (Smith et al., 1979; Seraj et al., 2012; Nikiforova 1982; Su et al., 2021). Moreover, previous studies found that plants in environments with high F– concentrations may have impacted growth, morphological, photosynthetic and metabolic characteristics (Reddy and Kaur, 2008; Bhargava and Bhardwaj, 2010; Bustingorri et al., 2016; Meng and Wu 1996; Gao et al., 1998; Elloumi et al., 2015; Zhong et al., 2014; Adeyeye et al., 2021)."**

(continued)

* https://www.cancer.org/cancer/risk-prevention/chemicals/water-fluoridation-and-cancer-risk.html
** https://www.frontiersin.org/journals/earth-science/articles/10.3389/feart.2022.1084890/full

How Radical Can RFK Jr. Be as America's Top Health Official?

Betsy McKay and Catherine Lucey, *Wall Street Journal*, November 16, 2024 (excerpt)

Robert F. Kennedy Jr. has pledged to make sweeping changes to public health if he is confirmed as the nation's top health official. He might hit some roadblocks along the way. As secretary of the Health and Human Services Department, Kennedy would oversee 13 operating divisions with more than 80,000 employees, including the Food and Drug Administration, National Institutes of Health and the Centers for Disease Control and Prevention.

The agencies set scientific standards and policies that are widely relied on by state and local authorities as well as international bodies. He would have "the power to reshape and reorganize every single agency under his jurisdiction," said Lawrence Gostin, co-faculty director of the O'Neill Institute for National and Global Health Law at Georgetown University.

"He would be able to strongly influence the public health recommendations that come out of those agencies," Gostin said.

But the 70-year-old environmental lawyer and vaccine critic is likely to face a tough confirmation process in the Senate. If he is confirmed, Kennedy would likely be forced to contend with legal limits, challenges and pushback from companies, scientists and doctors on some things he has promised, legal and public health experts said. "It is very difficult to drive seismic change quickly in a rulebound, lawbound bureaucracy," said Dan Troy, who was a chief counsel of the FDA under President George W. Bush.

Most public-health decisions in the U.S., including whether to fluoridate public tap water and which vaccines to recommend, are made by state and local authorities using federal guidance. About 72% of the U.S. population with access to public-water supplies in 2022 had fluoride levels that prevent tooth decay in their drinking water, according to the CDC. "It leaves a lot of latitude for jurisdictions," said Caitlin Rivers, an epidemiologist at the Johns Hopkins Bloomberg School of Public Health and author of the book "Crisis Averted," about the role of public health in fighting outbreaks.

John Crowley, chief executive officer of the Biotechnology Innovation Organization, a trade group, said he was eager to hear more of Kennedy's current views. "Everyone should recall that under President Trump's leadership we had remarkable success with Operation Warp Speed in the development of vaccines that literally saved the world," he said. "I'm confident that we can find common ground and work together ahead."

Kennedy would have power to make some but not all changes he has said he wants to make at the FDA. He could overrule the agency's decisions about drug approvals. It is a rare step, but in 2011, HHS Secretary Kathleen Sebelius overruled an FDA decision to allow an emergency contraceptive to be sold without a prescription to all women and girls, regardless of age. The matter landed in federal court, which ordered a lifting of age restrictions.

Kennedy has said he wants to fire FDA officials or eliminate its nutrition office. Civil servants have workplace protections. Troy, the former FDA chief counsel, stressed that at the agency only a tiny number of workers are typically political appointees. He said that writing a rule is a labor-intensive process that can take years and that removing a drug from the market can happen only through an "extensive legal process." Changing nutrition labels would be labor and time-intensive, Troy said, noting: "It took the FDA 15 years to define peanut butter."

"I don't really buy into the catastrophism on either side," he said.

Source: https://www.wsj.com/health/healthcare/rfk-jr-health-secretary-power-trump-cabinet-484e13d1

RFK Jr. Not an Ozempic Fan

Robert F. Kennedy, Jr., Posting on X, Sep 26, 2024

The MSM (mainstream media) cheerleading for Ozempic has begun! New op-ed in the NYT “Opinion | Is Obesity a Disease? It’s Complicated in the Age of Ozempic” does make a valid point: that weight-shaming is cruel, and that obesity is not a failure of character (we are not, she rightly and humanely states, suffering a “global breakdown in willpower”).

But that doesn’t mean obesity is something that just happens to us. The author never mentions our sickening food system based on a toxic industrial agriculture; in-the-tank government agencies; and the profitable manufacturing of poisonous and addictive processed foods—foods which have taken over our markets, restaurants, and school cafeterias.

Further, she doesn't mention the anxiety and crisis of meaning afflicting many of us—sufferings which tee us up to eat unhealthily. Nor does she mention the effect of excessive screen time, especially among our young people, and the sedentary lifestyles that accompany it. According to the writer, obesity seems to be a matter of lack—a lack of bariatric surgeries and a lack of Ozempic courtesy of Novo Nordisk, a Danish multinational whose wealth is bigger than Denmark’s entire economy. As this drug becomes more widely available, the journalist seems to suggest, “America’s biggest health problem” will be under control.

Instead of fixing our food system and addressing the obesity crisis at its root, the author focuses on a drug that may palliate the symptom – and gladden the wallets of distant Big Pharma execs. According to @calleymeans (who is not mentioned in this essay), “almost all of Novo Nordisk revenue is coming from taking advantage of Americans…the biggest target market for any drug in American history.” And this drug, according to Means, possibly causes harmful gastrointestinal, metabolic, and mental side effects (effects not mentioned in this essay). Regardless of possible side effects, some speculate this drug’s burgeoning market will make for a $1 trillion dollar company by 2030.

With a number like that, of course this drug is the answer! It has to be the answer. With a number like that, of course we don't talk about root causes; and about the need for better food and saner farming. Means again: “The second you get someone off the chronic disease treadmill, that’s not a profitable patient.”

Doctors say RFK Jr.'s Anti-Ozempic Stance Perpetuates Stigma and Misrepresents Evidence

Meg Tirrel, CNN, Nov 17, 2024

Robert F. Kennedy Jr. has pledged to tackle high rates of chronic diseases such as diabetes and obesity as President-elect Donald Trump's pick to lead the US Department of Health and Human Services. They're goals that many in the public health world find themselves agreeing with — despite fearing what else the infamous anti-vaccine activist may do in the post.

Just don't suggest that he tackle those goals with medications like Ozempic.

"They're counting on selling it to Americans because we're so stupid and so addicted to drugs," Kennedy said in an appearance with Fox News' Greg Gutfeld that he posted to Instagram last month, concluding that Ozempic, a wildly popular medicine approved to treat type 2 diabetes and used off-label for weight loss, is not going to "Make America Healthy Again."

Kennedy claimed that Novo Nordisk, which makes Ozempic, doesn't market the medicine in its home country of Denmark, where "they do not recommend it for diabetes or obesity; they recommend dietary and behavioral changes." In fact, Denmark does use Ozempic, so much so that the Danish Medicines Agency said in May that it would restrict its use until after people had tried less expensive medications to treat diabetes.

Kennedy said in the same appearance that the European Union "is right now investigating Ozempic for suicidal ideation," although the European regulator concluded in April that available evidence doesn't suggest Ozempic and other GLP-1 medicines cause suicidal thoughts or actions.

The US Food and Drug Administration, which Kennedy would oversee as HHS secretary, also reached that conclusion, although it's continuing to monitor for potential risk.

Those kind of confident but false or misleading assertions are Kennedy's signatures, said Dr. Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota. And they can be especially dangerous, he said, when applied to public health bedrocks like vaccines.

"He acts like he knows what he's talking about when he doesn't, and he says things with a definition that makes people convinced he has the data to support his statement," Osterholm told CNN. "Trying to follow him and understand what he's talking about is often like trying to nail Jell-O to the wall."

Kennedy's anti-vaccine stance put public health experts on edge even before Trump announced Thursday that Kennedy was his choice to run a department encompassing the FDA, the US Centers for Disease Control and Prevention, the National Institutes of Health, the Centers for Medicare and Medicaid Services and more.

Kennedy claims he's not anti-vaccine, but he has falsely said they cause autism, may cause more deaths than they prevent and could have sparked some of the world's deadliest pandemics.

Dr. Angela Fitch, co-founder and chief medical officer of Knownwell, a provider specializing in health care for people with obesity, said Kennedy's suggestion that diet and exercise alone can solve obesity "overnight" would set back hard-won efforts to better address the condition. "We've been trying to bust that stigma a lot of years," Fitch told CNN. "What we've heard a lot of in his rhetoric is, 'I want people to just eat less and exercise more.' And what we know is, that doesn't work."

Source: https://www.cnn.com/2024/11/17/health/rfk-jr-ozempic/index.html

RFK Jr.’s Vaccine Theories are ‘Cruel,’ Former CDC Director Says

Greta Reich, *Politico*, Nov 17, 2024 (excerpt)

Former CDC director Richard Besser critiqued President-elect Donald Trump’s pick of Robert F. Kennedy Jr. to lead the Department of Health and Human Services on Sunday, calling Kennedy “cruel” for continuing to push theories that vaccines can cause autism.

“This was a question that was asked and addressed decades ago, and to continue to lift that up is a cruel thing to do,” Besser said on ABC’s “This Week” to host Martha Raddatz.

Besser, the president and CEO of the Robert Wood Johnson Foundation, was the acting CDC director from January to June 2009.

“We should address chronic diseases — autism is one of those — and spend money trying to understand what are the causes of autism, and how can you address that,” he continued. “But to keep lifting up the idea that it has something to do with vaccination is really a cruel thing to do.”

Kennedy has long been an anti-vaccine activist, founding the anti-vaccine group Children’s Health Defense. He took leave from the group in 2023 to campaign for president.

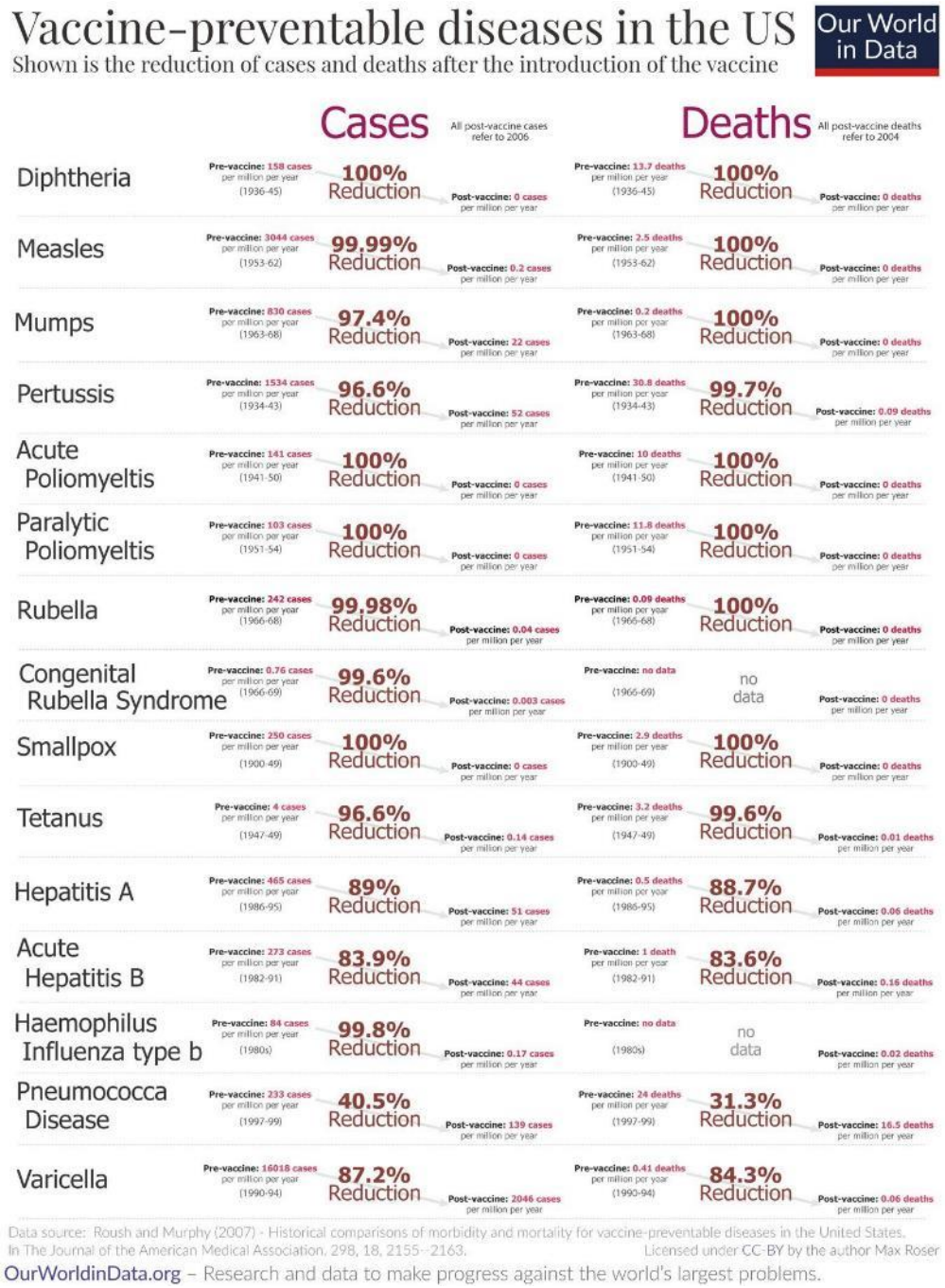
When asked about Kennedy’s record on vaccines — claiming that he would not take them away from anyone — Besser said it was less about taking them all away and more about the individualistic choices.

“It’s pushing the idea that vaccines should be something that is totally up to the individual,” he told Raddatz. “We have a social contract in our country. There are things we do for our own health, but there are things we do that are good for ourselves, our families and our communities, and vaccination falls into that category and having somebody who denies that in that role is extremely dangerous.”

“I am outraged because lives are at stake here,” Besser said.

Rich Besser
President
Robert Wood Johnson Foundation

Source: https://www.politico.com/news/2024/11/17/robert-kennedy-vaccine-theories-besser-00190034



Vaccines Are One of the Twentieth Century's Greatest Accomplishments

Rodrigues CMC, Plotkin SA. Impact of Vaccines; Health, Economic and Social Perspectives. *Front Microbiol*. 2020 Jul 14;11:1526.

In the 20th century, the development, licensing and implementation of vaccines as part of large, systematic immunization programs started to address health inequities that existed globally. However, at the time of writing, access to vaccines that prevent life-threatening infectious diseases remains unequal to all infants, children and adults in the world. This is a problem that many individuals and agencies are working hard to address globally. As clinicians and biomedical scientists we often focus on the health benefits that vaccines provide, in the prevention of ill-health and death from infectious pathogens. Here we discuss the health, economic and social benefits of vaccines that have been identified and studied in recent years, impacting all regions and all age groups. After learning of the emergence of SARS-CoV-2 virus in December 2019, and its potential for global dissemination to cause COVID-19 disease was realized, there was an urgent need to develop vaccines at an unprecedented rate and scale. As we appreciate and quantify the health, economic and social benefits of vaccines and immunization programs to individuals and society, we should endeavor to communicate this to the public and policy makers, for the benefit of endemic, epidemic, and pandemic diseases.

Vaccine	Peak cases in prevaccine era (year)	Vaccine coverage in children 19–35 months old (% [95% CI])	Cases in 2017 (*n*)	Disease reduction (%)
Smallpox	110,672 (1920)	–	0	100
Diphtheria	30,508 (1936)	94.0 (93.3 – 94.7)	0	100
Measles (non-imported)	763,094 (1958)	91.5 (90.6 – 92.3)	99	99.99
Mumps	212,932 (1964)	91.5 (90.6 – 92.3)	6,109	97.13
Rubella	488,796 (1964)	91.5 (90.6 – 92.3)	7	100.00
Congenital rubella syndrome	20,000 (1964 – 65)	–	5	99.98
Pertussis	265,269 (1934)	94.0 (93.3 – 94.7)	18,975	92.85
Polio (paralytic)	21,269 (1952)	92.7 (91.9 – 93.5)	0	100
Tetanus	601 (1948)	94.0 (93.3 – 94.7)	33	94.51

Source: https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.01526/full

There is Potential to See an NIH Critic (and Big RFK Jr. Supporter) Bhattacharya In Charge of the NIH

Dr. Bhattacharya does not look like a strong ally for scientific innovation, expressing conspiratorial views of the role of regulators relative to vaccines – and looking to refight Pandemic decisions four years too late. In many ways he appears to be the opposite of current NIH director Monica Bertignolli.

Jay Bhattacharya, an NIH critic, emerges as a top candidate to lead the agency

The Stanford physician was excoriated by NIH's director in 2020 for his "fringe" ideas on covid. Four years later, he's poised for power in Trump's Washington.

12 min 249

Washington Post, Nov 16, 2024

Stanford University physician and economist Jay Bhattacharya, whose views on the coronavirus pandemic response proved controversial, could be poised for a major health agency role in the Trump administration. (Anthony Behar/Sipa USA/AP)

By Dan Diamond

Source: https://www.washingtonpost.com/health/2024/11/16/nih-director-jay-bhattacharya-covid-great-barrington-declaration/

Jay Bhattacharya and Kevin Bardosh, *Unherd*, Nov 15, 2024

The rot, having accumulated over decades, was plain for all to see. The National Institutes of Health (NIH), whose annual budget is $45 billion, orchestrated under the leadership of Francis Collins and Anthony Fauci a massive suppression of scientific debate and research. The Centers for Disease Control and Prevention (CDC) exaggerated risk and issued policy guidance with little evidence in support of unprecedented vaccine mandates. **The Food and Drug Administration (FDA)'s conflicts of interest with the pharmaceutical industry meant vaccines and therapeutics were approved with little to no evidence, sometimes based on faulty modelling.** And the Biden administration pushed all of this with orchestrated PR campaigns, spreading falsehoods and misinformation.

Clearly, the status quo is no longer tenable. Trust in American physicians and hospitals dropped from 71% to 40% between 2020 and 2024, according to a July study in JAMA. A Covid-era political realignment facilitated Trump's electoral win last week, with a coalition that included disenchanted Left-liberals who rejected the centralised power of scientific bureaucrats and found an ally in Kennedy. Yet the officials continue to deny their own culpability, avoiding a long look in the mirror.

Kennedy can be that mirror. A successful environmental lawyer and erstwhile darling of the centre-left — so much so that Barack Obama floated him to lead the Environmental Protection Agency in 2008 — he is the most high-profile figure to tackle these problems head-on. His rebranding of MAGA to Make America Healthy Again (MAHA) can carry broad appeal for Americans.

Source: https://unherd.com/newsroom/rfk-jr-will-disrupt-the-us-medical-establishment/.
Also see https://www.newsweek.com/rfk-reforms-should-embraced-doctors-stanford-professor-1986825

Substantial Contradictions Within Trump Advisors on Health Policy

Arthur Allen, *KFF Health News*, Nov 15, 2024

"Never has anybody like RFK Jr. gotten anywhere close to the position he may be in to actually shape policy," said Lewis Grossman, a law professor at American University and the author of "Choose Your Medicine," a history of U.S. public health. Kennedy and an adviser Calley Means, a health care entrepreneur, say dramatic changes are needed because of the high levels of chronic disease in the United States. Government agencies have corruptly tolerated or promoted unhealthy diets and dangerous drugs and vaccines, they say.

At meetings last week at Mar-a-Lago involving Elon Musk, Tucker Carlson, Donald Trump Jr., Kennedy, and Means, according to *Politico*, some candidates for leading health posts included Jay Bhattacharya, a Stanford University scientist who opposed covid lockdowns; Florida Surgeon General Joseph Ladapo, who opposes mRNA covid vaccines and rejected well-established disease control practices during a measles outbreak; Johns Hopkins University surgeon Marty Makary; and Means' sister, Stanford-trained surgeon and health guru Casey Means.

Trump's health influencers are not monolithic. Analysts see potential clashes among Kennedy, Musk, and more traditional GOP voices. Casey Means, a "holistic" MD at the center of Kennedy's "Make America Healthy Again" team, calls for the government to cut ties with industry and remove sugar, processed food, and toxic substances from American diets. Republicans lampooned such policies as exemplifying a "nanny state" when Mike Bloomberg promoted them as mayor of New York City.

Both the libertarian and "medical freedom" wings oppose aspects of regulation, but Silicon Valley biotech supporters of Trump, like Samuel Hammond of the Foundation for American Innovation, have pressed the agency to speed drug and device approvals, while Kennedy's team says the FDA and other agencies have been "captured" by industry, resulting in dangerous and unnecessary drugs, vaccines, and devices on the market. Kennedy and Casey Means want to end industry user fees that pay for drug and device rules and support nearly half the FDA's $7.2 billion budget. It's unclear whether Congress would make up the shortfall at a time when Trump and Musk have vowed to slash government programs. User fees are set by laws Congress passes every five years, most recently in 2022.

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Source: https://kffhealthnews.org/news/article/trump-rfk-maha-federal-health-agencies-takeover/

There is so much about the prospect of having RFK Jr. in at HHS that is surreal.

Perhaps one of the most surreal things is that, in some ways, he is aggressively touting ideas that have been derided by conservatives before (for example, when Mike Bloomberg tried to tax sugary soft drinks when Mayor in NYC).

A similar set of ideas regarding food, exercise and chronic disease was promoted by Michelle Obama while she was in the White House. She did not get support at the time from Republicans.

Even odder are RFK Jr's. comments on industry capture of regulatory agencies. Based on our experience it seems most unlikely to be true, but if one saw the arguments without their source, they could just as easily be coming from Bernie Sanders. Except that Sanders doesn't talk about vaccines and autism.

It feels most unlikely to us that Trump tolerates this type of anti-business stance for long.

Vivek Ramaswamy Also Taking an Interest in FDA Policy

While sitting in the White House, Ramaswamy will be in a position to influence FDA. As a sophisticated biotech market observer, his thoughts will obviously be relevant in a Trump administration and are more intelligent than conspiracy theories about fluoride and vaccination that are not based on evidence. It will be interesting to see how much influence he gets. As for the issues below, some like accepting China data packages, are in the purview of the FDA while others, like requiring two phase 3 clinical studies for approval are implied by statute and largely non-discretionary for FDA. The implied policy actions discussed here could be positive for the biotech sector.

Vivek Ramaswamy on X, Nov 15, 2024

My #1 issue with FDA is that it erects unnecessary barriers to innovation (e.g. two replicate phase 3 studies instead of one, refusal to accept valid clinical results from other nations, etc.).

This stops patients from accessing promising therapies & raises prescription drug costs by impeding competition.

The agency's staff have callous disregard for the impact of their daily decisions on the cost of developing new therapies, which inevitably gets passed on to the healthcare system. That's the actual problem with FDA & it's the one we should be talking more about.

Vivek Ramaswamy

Bill Ackman and Yair Einhorn See A Big Jump in Biopharma M&A Coming in Trump Administration

Yair Einhorn @yaireinhorn · 1h

President Trump's victory could have a huge impact on sectors in which deals have been held back by the regulators - such as Pharma & BioTech. If @BillAckman is correct - we could witness an unprecedented increase in M&A deals in these sectors. Now let's hope Bill is right! $XBI

Vivek Ramaswamy @VivekGRamaswamy · Nov 15

My #1 issue with FDA is that it erects unnecessary barriers to innovation (e.g. two replicate phase 3 studies instead of one, refusal to accept valid clinical results from other nations, etc.). This stops patients from accessing promising therapies & raises prescription drug

Punnett Square Capital @punnettsqrcap · Nov 16

Peter, how do you think RFK Jr as HHS Sec may impact biotech?

1 239

Peter Kolchinsky @PeterKolchinsky · Nov 16

Too early to tell. Innovation has many defenders. Most people know that medicines save lives. It's not really a partisan issue behind the scenes.

1 4 229

Show replies

Source: https://x.com/yaireinhorn

Thoughtful Perspective from Drew Armstrong of *Endpoints News*

Drew Armstrong, Post-Hoc Column, *Endpoints News*, Nov 15, 2024

In stark contrast to Kennedy, Ramaswamy has called for less stringent reviews of drugs and faster approvals. On Friday in a social media post, the former pharma CEO said his "#1 issue with FDA is that it erects unnecessary barriers to innovation (e.g. two replicate phase 3 studies instead of one, refusal to accept valid clinical results from other nations, etc.)."

The merits of Ramaswamy's ideas aside (and the fact that in many cases, two Phase 3 trials aren't used for approval), the two represent almost entirely different philosophies about the biopharma industry. Kennedy sees the industry as dangerous and corrupt, and in need of far greater oversight and restriction by the government. Ramaswamy appears to see the government as the problem, holding back an industry that should deal with far less interference. Those views aren't compatible.

We are in the very, very early days of the eventual Trump White House. And if there have been many constants to the volatile politics of his administration, it's that what seems true today might not be tomorrow. A huge amount will change — people, ideas, positions, priorities. Kennedy may not survive the nomination process (he's already generating opposition from anti-abortion advocates, and the agricultural industry allies in the Senate haven't gotten started yet). Ramaswamy may run into the dull buzzsaw of inertia that is the US federal bureaucracy and find that making huge cuts to regulation and people is easier said than done.

I don't know how this ends. But I do know it's far from settled.

Drew Armstrong, Executive Editors, Endpoints

Source: https://endpts.com/what-is-the-future-of-the-trump-admins-pharmaceutical-policies/

The Macro Situation Remains Paramount to Biotech

Last week saw the release of October 2024 CPI data for the U.S. market. The CPI rose by 0.2% in October – given inflation an annualized rate of 2.4%.

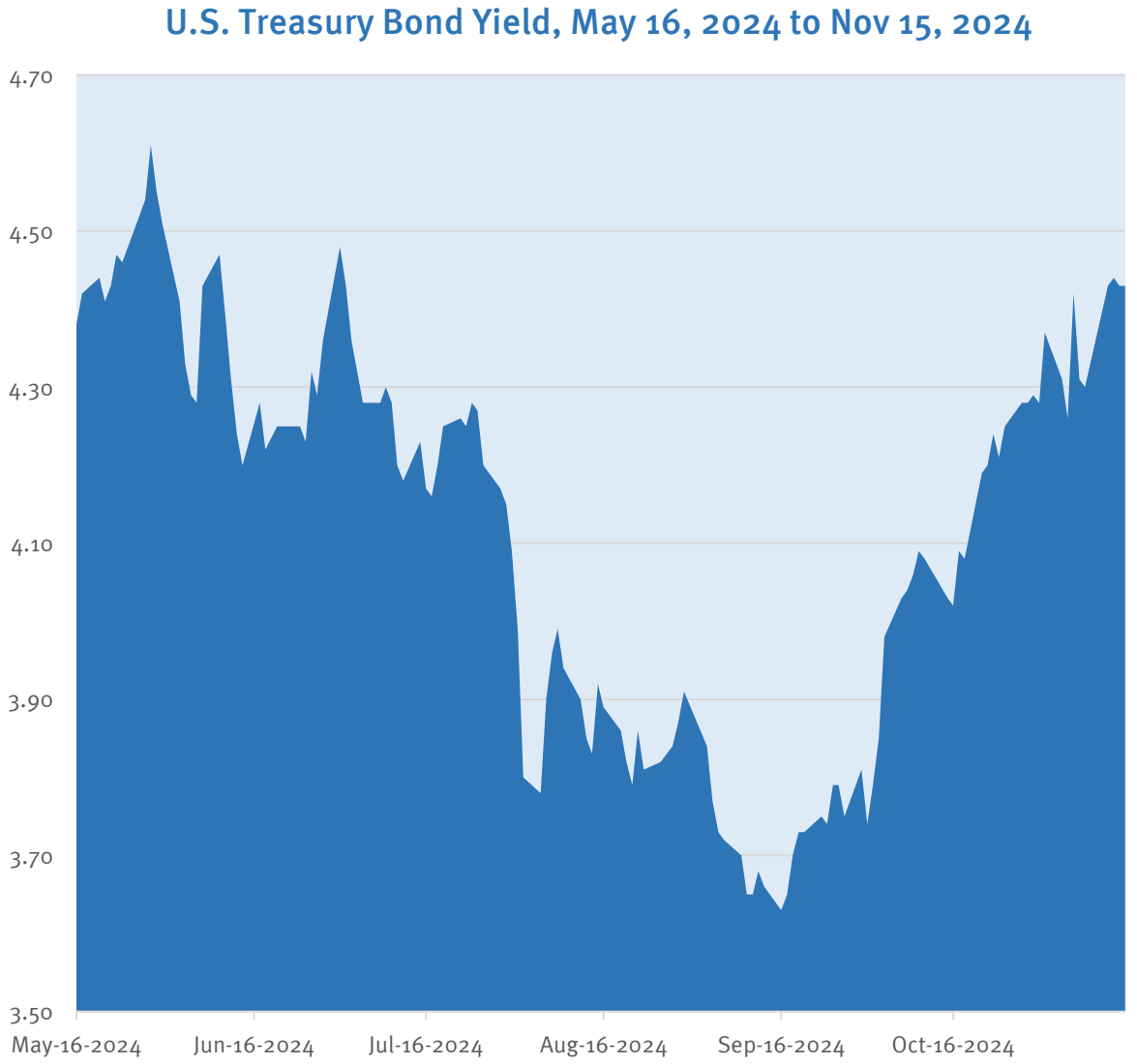
Overall, this is good news. Inflation is very much coming under control.

However, the Fed remains cautious following two rate cuts and wants to see more inflation numbers come in.

An article last week by AP noted:

"Chair Jerome Powell said Thursday that the Federal Reserve will likely cut its key interest rate slowly and deliberately in the coming months, in part because inflation has shown signs of persistence and the Fed's officials want to see where it heads next. Powell, speaking in Dallas, said that inflation is edging closer to the central bank's 2% target, 'but it is not there yet.' At the same time, he said, the economy is strong, and the policymakers can take time to monitor the path of inflation."

We've gone from "higher for longer" to "slower for longer" you might say. This is clear enough in the chart at right that shows the recent retracement in the 10-Year U.S. Treasury Yield. With a yield of 4.4% we are looking at interest rates that are nearing the high point of the last six months.



Source for Treasury Data: S&P CapitalIQ. Source for Fed quote: https://apnews.com/article/federal-reserve-inflation-economy-trump-election-rates-ofbe8b37fad39e03ded3bfc87d9ccc9f

Taxation Also Highly Relevant to Biopharma Industry

While many in our industry recoil in horror at the prospect of RFK at HHS, Bhattacharya at NIH and who knows who at FDA, there is potential for substantial upside for pharma investors embedded in prospective Trump Administration policies.

We have written before about what happened to the market after Ronald Reagan's election in 1980 and what might happen after a Trump election.

The parallels are obvious:

1. Reagan came in after a period of inflation and Fed tightening
2. Investors in the market were dispirited and failed to react even to positive news when it arrived.
3. Some Reagan cabinet appointees were highly controversial - such as James Watt a pro-development advocate to Secretary of Interior; Ed Meese (previously accused of ethical lapses) to Attorney General; Anne Gorsuch Burford to Head of EPA; and William Bennet to the Department of Education (an advocate of funding cuts in education).*
4. U.S. society was highly divided, and Reagan ran an election with thinly veiled racist advertisements.
5. The U.S. populace was highly aroused about immigration, Iranians and inflation.

There are, of course, many differences as well.

For one, this is Trump's second time in office. Further, while pro-business, Trump did not display the same zeal for cutting government spending as did Reagan. Reagan also faced a divided Congress. The House remained Democratically controlled throughout his Administration.

What was most interesting was that soon after coming into office, Reagan engineered the passage of the Economic Recovery Tax Act of 1981. This was a tax cut package like that put in place by John F. Kennedy after his election.

The package's key ingredient was a 25% reduction in marginal tax rates across the board over three years. This included accelerated depreciation schedules and investment tax credits aimed at encouraging capital investment.

This fiscally expansionary policy had the desired effect:

1. Real GDP growth averaged about 3.5% annually during Reagan's presidency, rebounding strongly after the early 1980s recession.
2. There was a massive rally in the market. In the 20 years after Reagan's election, the stock market rose by nine times.

There really wasn't anything like the NBI or XBI to allow us to comment on what it meant for biotech, but we would note that the Reagan era was a very good period for the pharma industry.

* Watt didn't last long, ultimately resigning over insensitive comments. He stated that a government commission was diverse by having "a black, a woman, two Jews, and a cripple." Burford was also out quickly after a scandal emerged involving her actions with the EPA SuperFund program.

Reagan Era Tax Cuts Supercharged the Markets

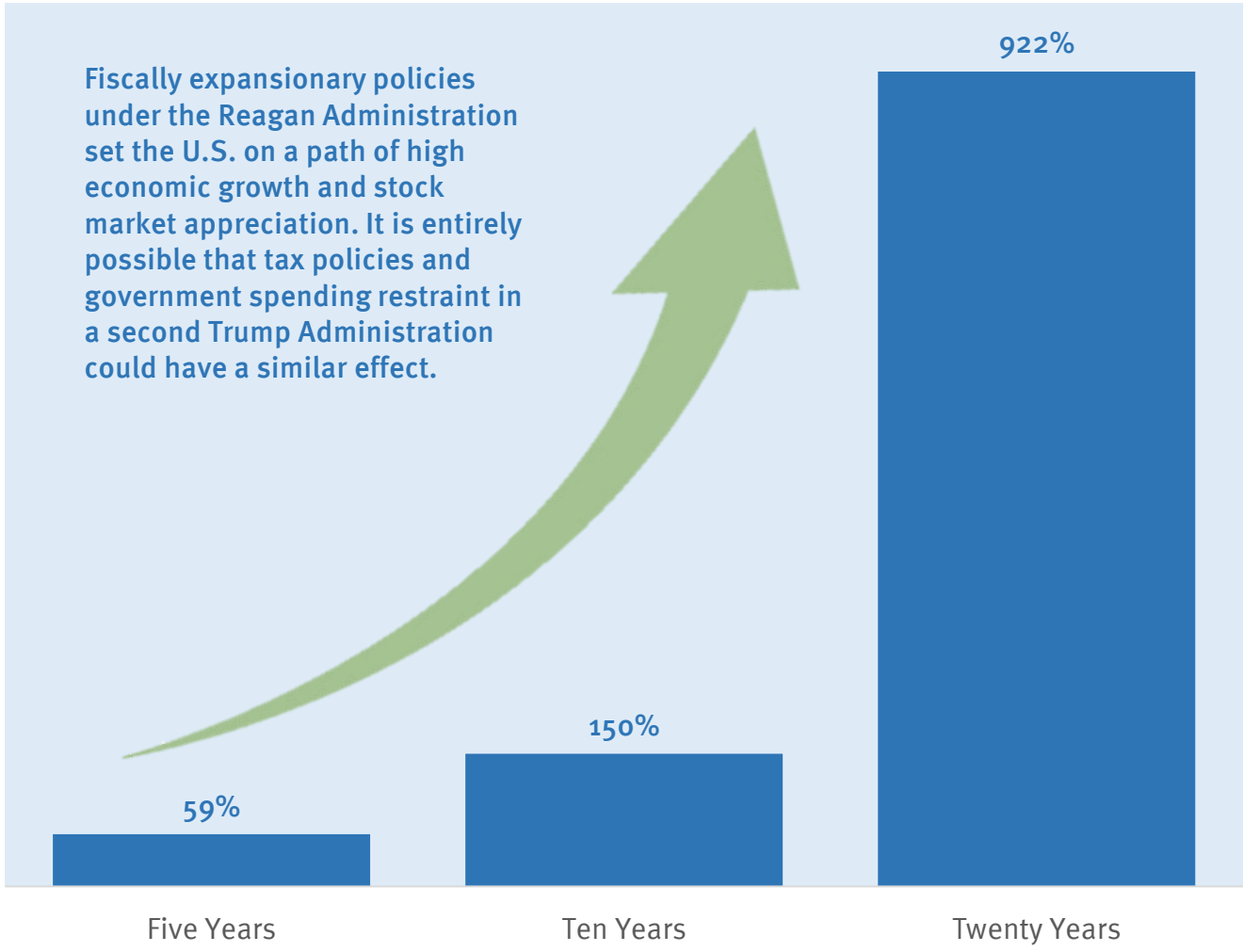
Marq Niquette and Enda Curran wrote in *Bloomberg* on Nov 15, 2024:

> "The Republican sweep of the presidency and Congress has transformed what could have been a struggle to merely renew Donald Trump's tax cuts into a multi-pronged campaign to slash levies in new and bigger ways. The incoming Republican majorities in the House and Senate mean Trump can enact a tax bill without making concessions to Democrats. Republicans will only be constrained by how much deficit spending the party's lawmakers and global financial markets can tolerate. Trump enthusiastically promoted both the corporate-rate reduction and the break for tipped income during the presidential campaign and also promised myriad other tax breaks."

It looks highly likely that we will see major tax reductions come through in the first six months of Trump's Presidency.

We think that is likely to drive the market up overall and, to the extent that Trump can control deficit spending, there could be even further benefit.

S&P 500 Performance in the Period After Reagan's Election



The Long Run Picture

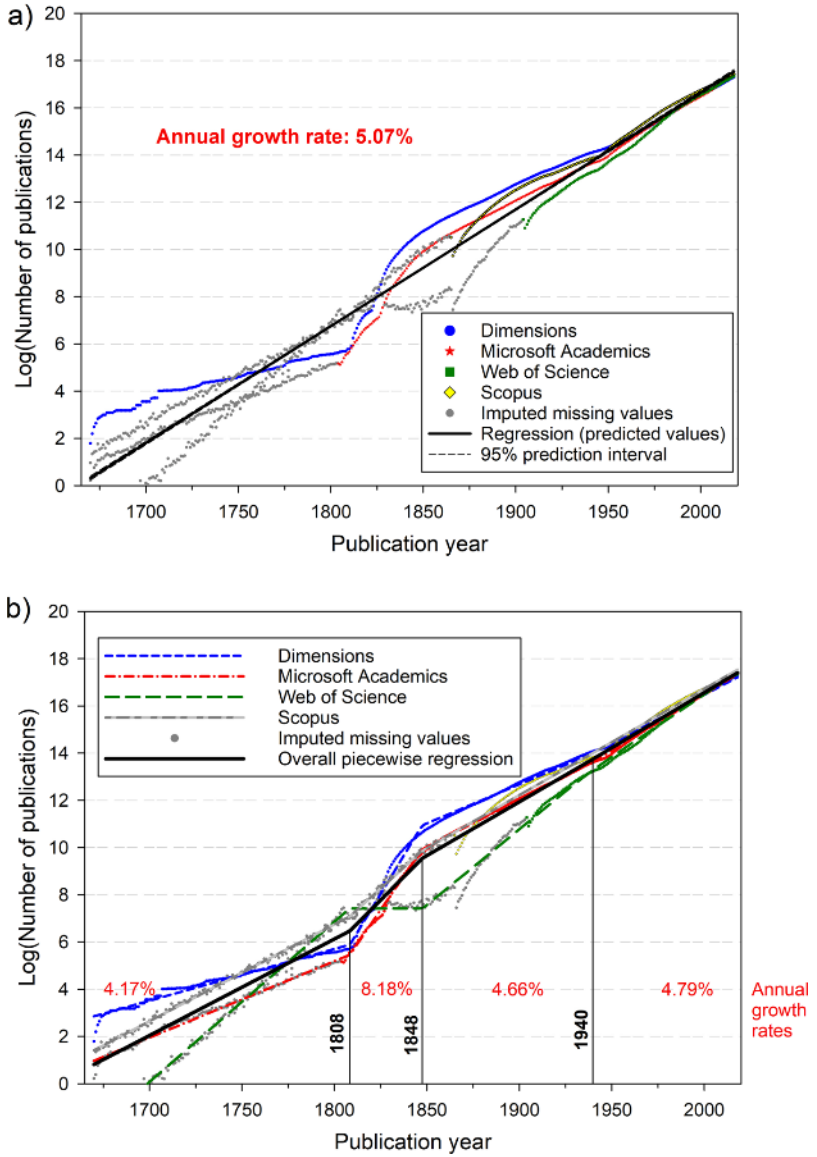
Putting aside politics and the arguments made by both sides of the political aisle, it is important to note the obvious:

1. RFK Jr at HHS or not, the long-term trend of scientific innovation is likely to continue for decades to come. One way to think about this is look at publication counts of life science publications going back to 1650 (see charts at right). The rate of expansion in publications has been relatively steady for Centuries, reflecting the addition of scientific discoveries triggered by previous discoveries. The long-term annual growth rate of publication count has been about five percent for the last 170 years. This momentum dates to the Renaissance and has been unabated despite periodic retrograde political policies, inquisitions, wars and the like.
2. The long-term growth of the pharma industry is unlikely to abate. Recall that previously shared statistics show that the top 15 players in the pharma industry have grown by eight times in real terms over the last 50 years and are likely to double or triple in size over the next 20.
3. We are seeing expansion of the modalities of innovation, acceleration of techniques to translate scientific breakthroughs to pharmaceutical products and countless important biological discoveries.

The ultimate reason not to worry about the Trump Administration is that innovation is the only fundamental for our sector that matters in the long run. The economics of drug pricing matter. Tax policy matters. The NIH matters. The FDA matters. We should treasure our industry's institutions and encourage society to pay for therapeutic interventions.

But what really matters in the long run is innovation. The level XBI in ten years will depend much less on who runs the FDA for the next four years and much more on how well our industry can innovate and translate scientific ideas into therapeutics.

Number of Life Science Publications Growing at 5% Annually, 1650 to Present



Source: Bornmann, L., Haunschild, R. & Mutz, R. Growth rates of modern science: a latent piecewise growth curve approach to model publication numbers from established and new literature databases. *Humanit Soc Sci Commun* **8**, 224 (2021)

The Case for Investment in Biotech in Nov 2024

There is so much to be optimistic about in our industry. These positives are highlighted at right and in the charts from a talk we gave a few weeks ago (on the next page).

Despite these positives, political involvement is going to be incredibly important for industry participants over the next four years:

1. We need to push back on ideas espoused by policymakers that are not backed by science.
2. We need to work together to do our best to roll back the IRA and its most harmful provisions.
3. We need to work together to push back on senseless approaches to cost-effectiveness analysis for drugs built into the IRA.*
4. We need to do our utmost to protect value-additive institutions, including the FDA, the CDC and the NIH.

Ultimately, if we are effective as an industry, we expect that the future of biopharma will be even brighter four years from now than it is today.

Historical returns in biotech investment have been well above market averages	Valuations remain attractive – despite risks posed by Trump policies	Macroeconomic picture is Improving
Upside of possible Trump policy is not priced into biotech at all	Potential change in IRA and FTC particularly positive for biotech industry	Upside of Trump tax policies not priced into the market at all
Pharma has to acquire biotechs – pharma can't innovate enough on its own	Growth in medical spend will accelerate over time faster than the overall economy	The ultimate fundamental is incredibly positive - innovation

* See, for example, https://rapport.bio/all-stories/the-way-forward-for-therapeutics-value-assessment.

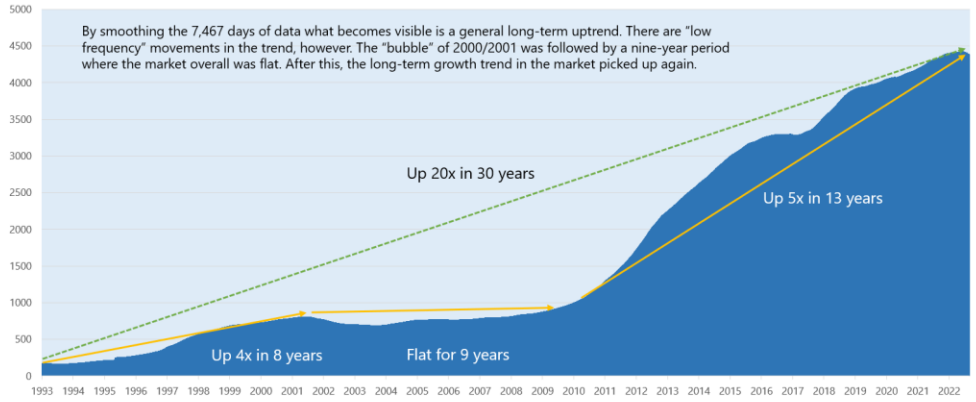
Some Charts from a Recent Talk

Some slides from a recent talk to a group of investors in a biotech venture fund

Biotech Up Big in the Long Run

When one looks at the underlying market trend, it's very clear that biotech investing involves a long-term uptrend. But one must be prepared for occasional long periods of flat performance.

Nasdaq Biotech Index, Centered Moving Average of 1200 Days, Nov 1993 to June 2023



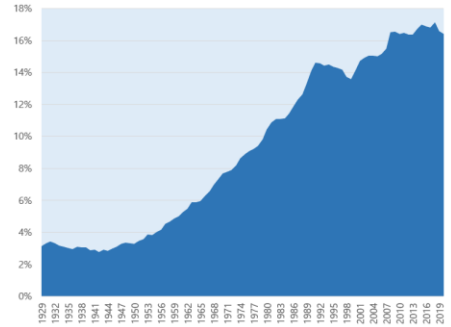
Source: CapitalIQ

15

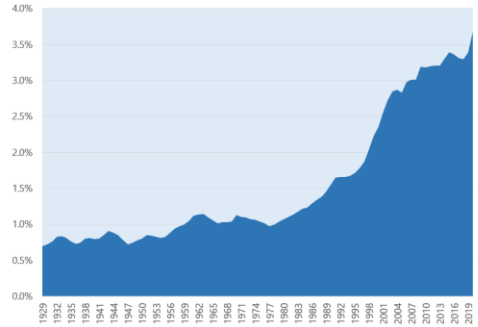
Medical Spending Rises Disproportionately with National Income

The U.S. Consumer has spent an increasing percentage of wallet on medical care. Once the consumer has covered the basics of food and shelter, he/she directs the marginal dollar to superior goods such as investment in life extension (medical care).

Healthcare Spend in the US / Total Economy Expenditures, 1929 to 2020



Pharma Spend in the US / Total Economy Expenditures, 1929 to 2020

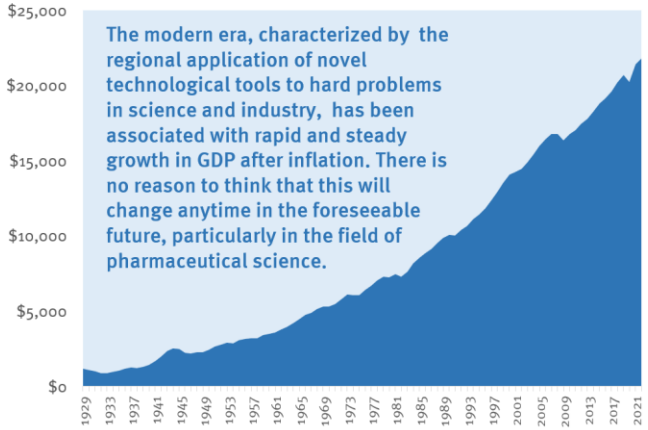


Source: National Income and Product Accounts of the United States.

16

Pharma Sector Will *Triple* in Size by 2050 (Real $)

U.S. Real GDP, 1929 to 2022 (Billions, 2017 Dollars)



PWC forecasts that the U.S. economy will grow at 1.8% per annum in real terms through 2050.

The global economy will grow faster.

Using the econometric relationship between GDP growth and pharma spend, we should expect to see U.S. pharma spend nearly double by 2050 (only 27 years to go) and global pharma spend more than triple.

Source: National Income and Product Accounts of the United States.

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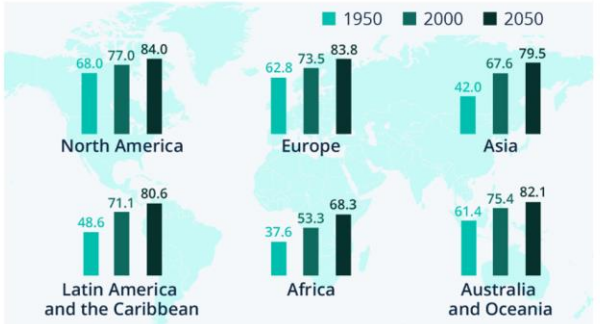
Longer Lives Imply Yet Further Medical Spend

Because humans are living longer, they necessarily need to spend more money on medicines – independent of their incomes.

- As persons live longer in industrialized countries their lifetime demand for pharmaceutical and other medical products will rise rapidly.
- As therapies continue to come online to treat these diseases persons are increasingly likely to face second, third- and fourth-line chronic disease states – particularly diseases of the aged such as Alzheimer's disease and cancer.

Life Expectancy at Birth, 1950 to 2050 by Region



* median estimates; as of 2022

Source: United Nations Population Division

Source: OECD Health Statistics, 2011.

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Biopharma Market Update

The XBI Closed at 91.8 Last Friday (Nov 15), Down 11.9% for the Week

The XBI was down substantially last week on concerns for the biopharma industry associated with the appoint of RFK Jr. to run the Department of Health and Human Services. This was one of the largest drops we have seen in several years. The XBI now is up only 2.8% for the year.

Biotech Stocks Down Last Week

Return: Nov 9 to Nov 15, 2024

Nasdaq Biotech Index: -10.2%
Arca XBI ETF: -11.9%
Stifel Global Biotech EV (adjusted): +6.1%*
S&P 500: -2.1%

Return: Dec 29, 2023 to Nov 15, 2024 (YTD)

Nasdaq Biotech Index: +0.7%
Arca XBI ETF: 2.8%
Stifel Global Biotech EV (adjusted): +43.8%*
S&P 500: +23.1%

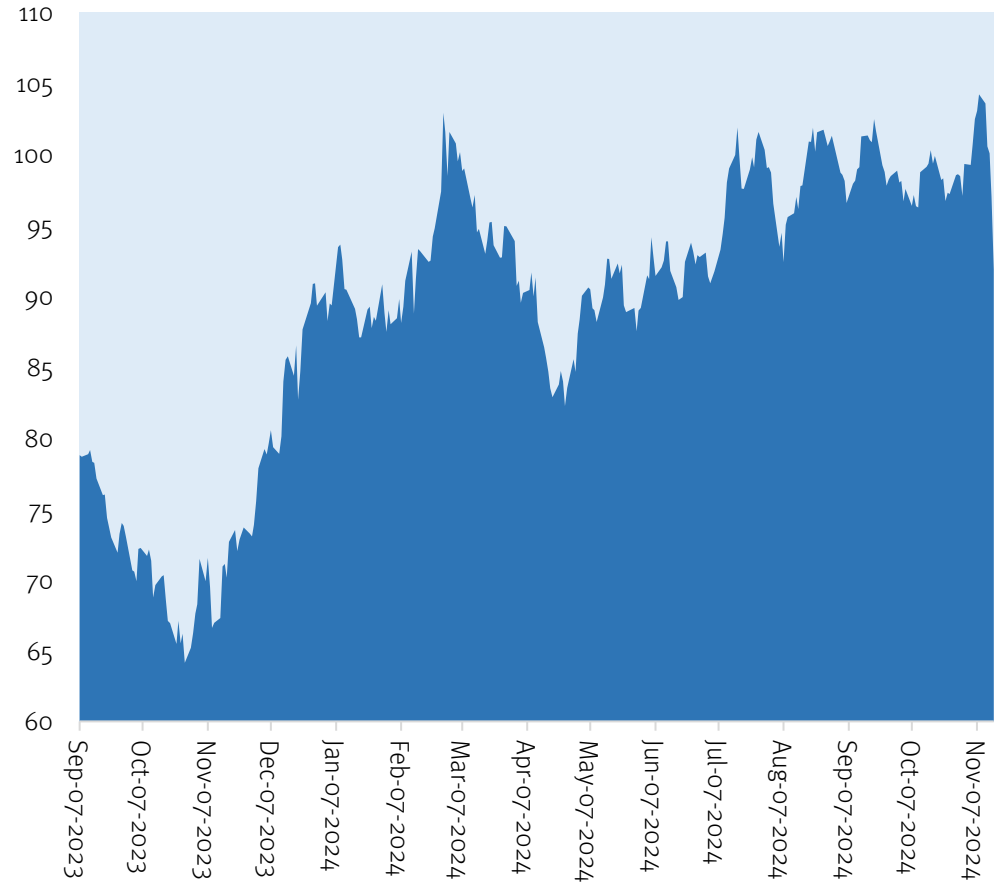
VIX Down

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%
Nov 15, 2024: 16.1%

10-Year Treasury Yield Up

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%
Nov 15, 2024: 4.43%

XBI, Sep 7, 2023 to Nov 15, 2024

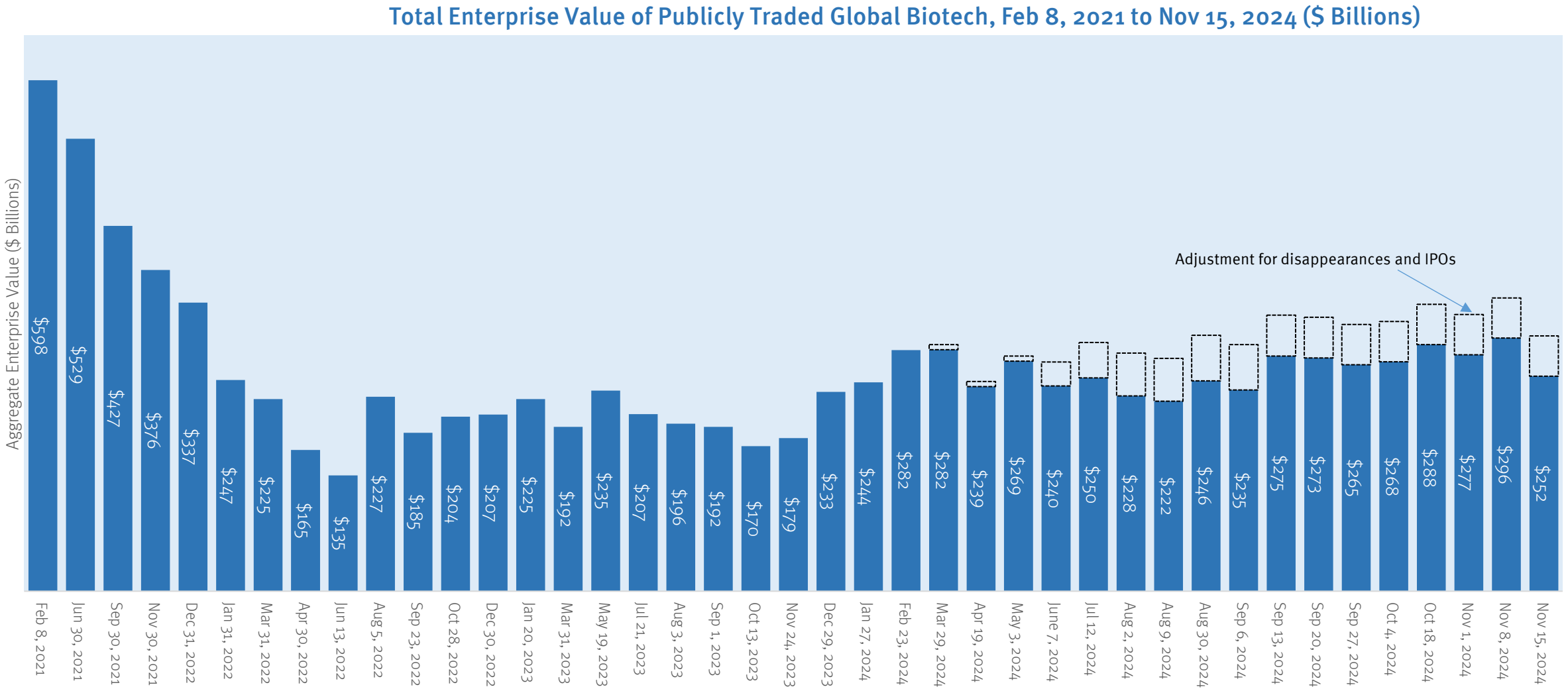


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs. The annual change by market cap is even higher.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down 15% Last Week

Biotech stocks dropped 15% in the last week. On a disappearance adjusted basis, biotech is up 28% for the year to date (enterprise value). Summit Therapeutics is now the only biotech in the world with an EV over $10 billion.

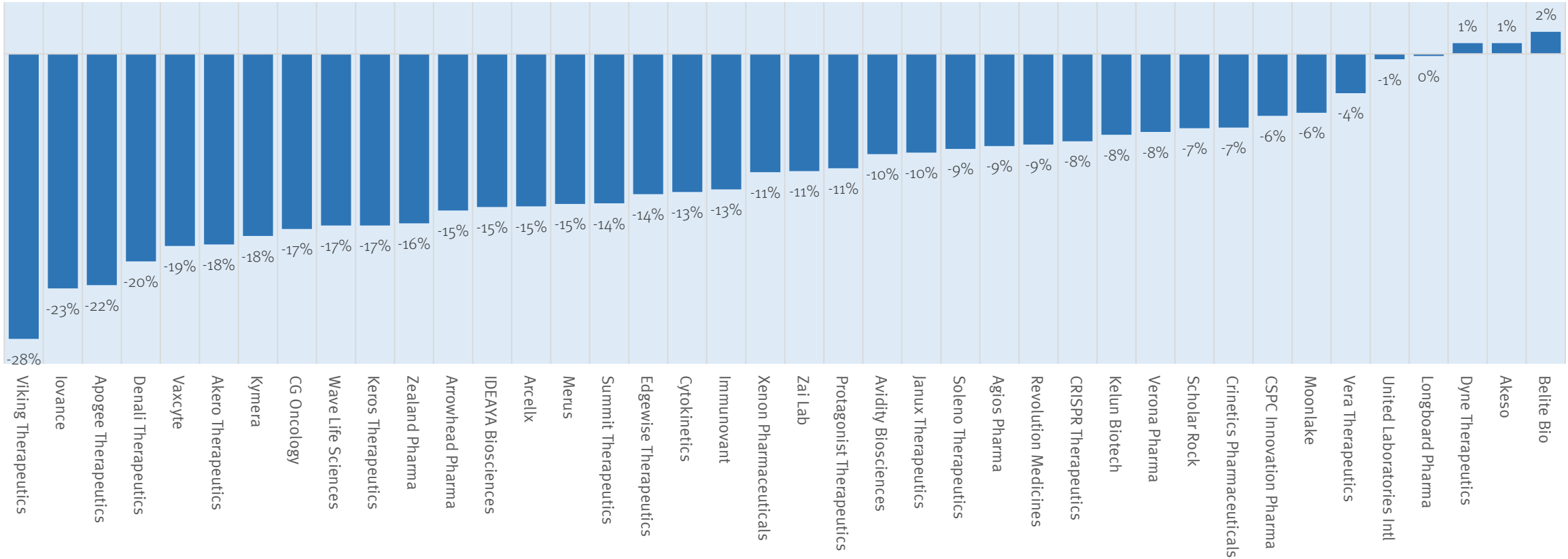


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

An Ugly Week for Global Biotech

This chart shows the percent change in share price last week for the top 40 biotechs worldwide by their market cap at start of week. The median change in value was -11%. Viking, Apogee, Iovance and Denali were hit particularly hard. We track public 763 biotechs worldwide. Last week 18% saw their share price rise while 82% saw their share price decline. In total 43% saw their shares drop by 10% or more and 14% saw their shares drop by 20% or more.

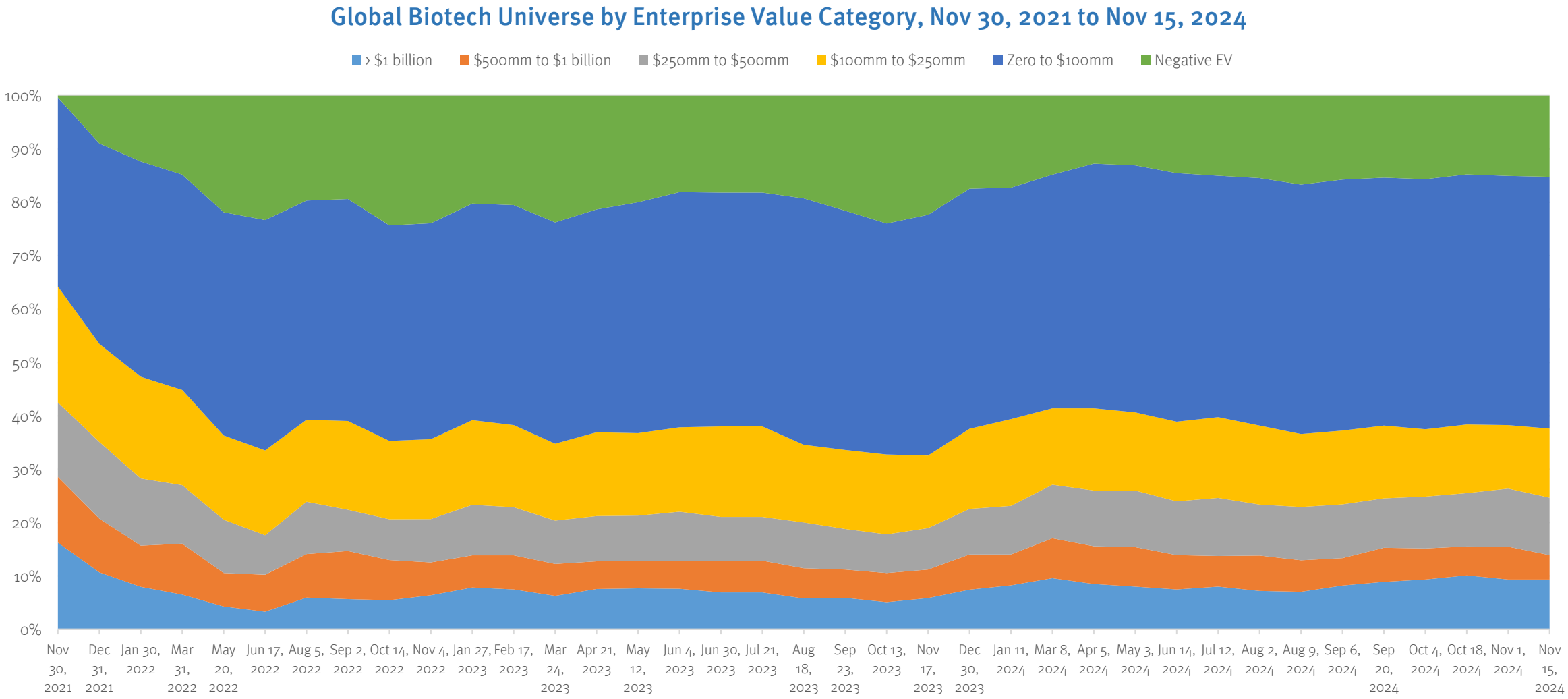
Share Price Return for Week Ended Nov 15, 2025 of Top 40 Global Biotechs by Market Cap (start of week)



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

Global Biotech Neighborhood Analysis

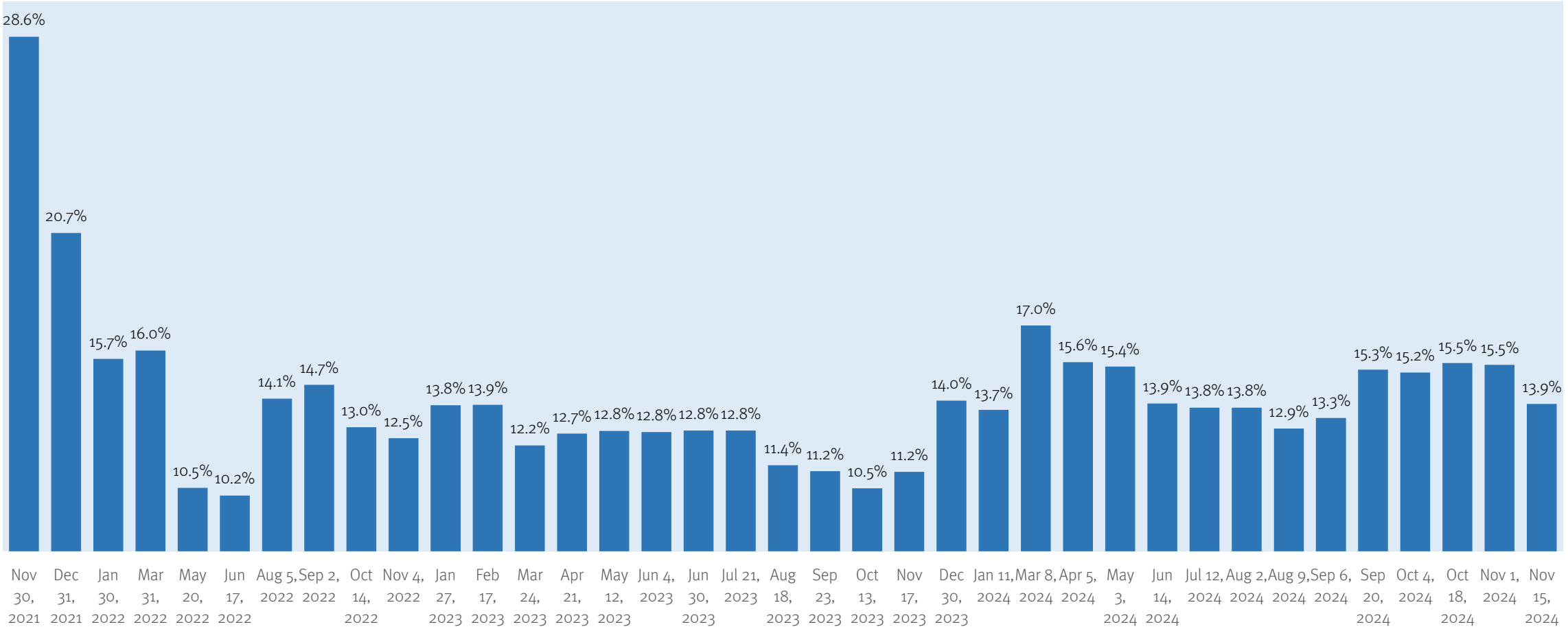
The population of high valued biotechs has shrunk meaningfully in the last week.



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

The Percent of Biotechs Worth More than $500 Million Has Dropped Precipitously in Just a Few Days

Percent of Biotechs with an Enterprise Value of $500mm or More, Nov 2021 to Nov 2024



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

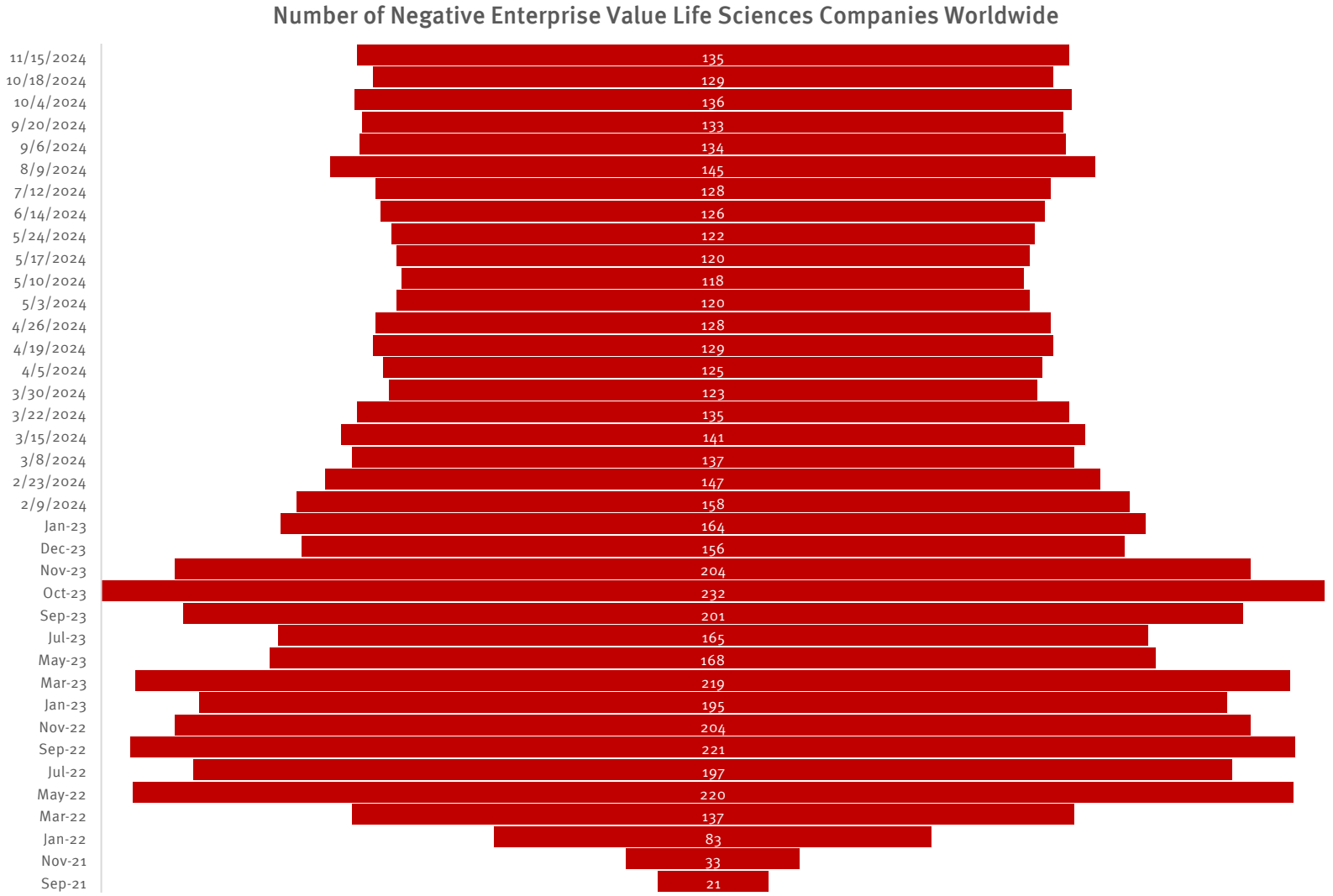
Life Sciences Sector Lost $571 Billion in Value Last Week (5.7%)

We don't remember the last time the life sciences sector peeled off so much value in one week. The RFK Jr. bear market did not spare any sector, although biotech and HCIT were particularly hard hit.

Sector	Firm Count	Enterprise Value (Nov 15, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	79	$93,731	-3.7%	-2.6%	13.4%
Biotech	774	$249,398	-15.2%	-10.9%	-5.1%
CDMO	39	$158,389	-6.7%	-5.9%	3.5%
Diagnostics	81	$240,414	-1.9%	-2.9%	-2.8%
OTC	29	$24,908	-3.6%	-6.2%	-8.2%
Commercial Pharma	712	$6,085,923	-6.3%	-10.0%	8.0%
Pharma Services	38	$167,051	-7.1%	-8.3%	-17.3%
Life Science Tools	50	$640,281	-6.8%	-11.4%	7.4%
Devices	180	$1,789,997	-2.0%	-0.1%	19.9%
HCIT	10	$21,353	-12.1%	-4.4%	5.3%
Total	**1992**	**$9,471,445**	**-5.7%**	**-8.1%**	**10.0%**

Source: CapitalIQ and Stifel analysis

Count of Negative Enterprise Value Life Sciences Companies Has Risen Slightly

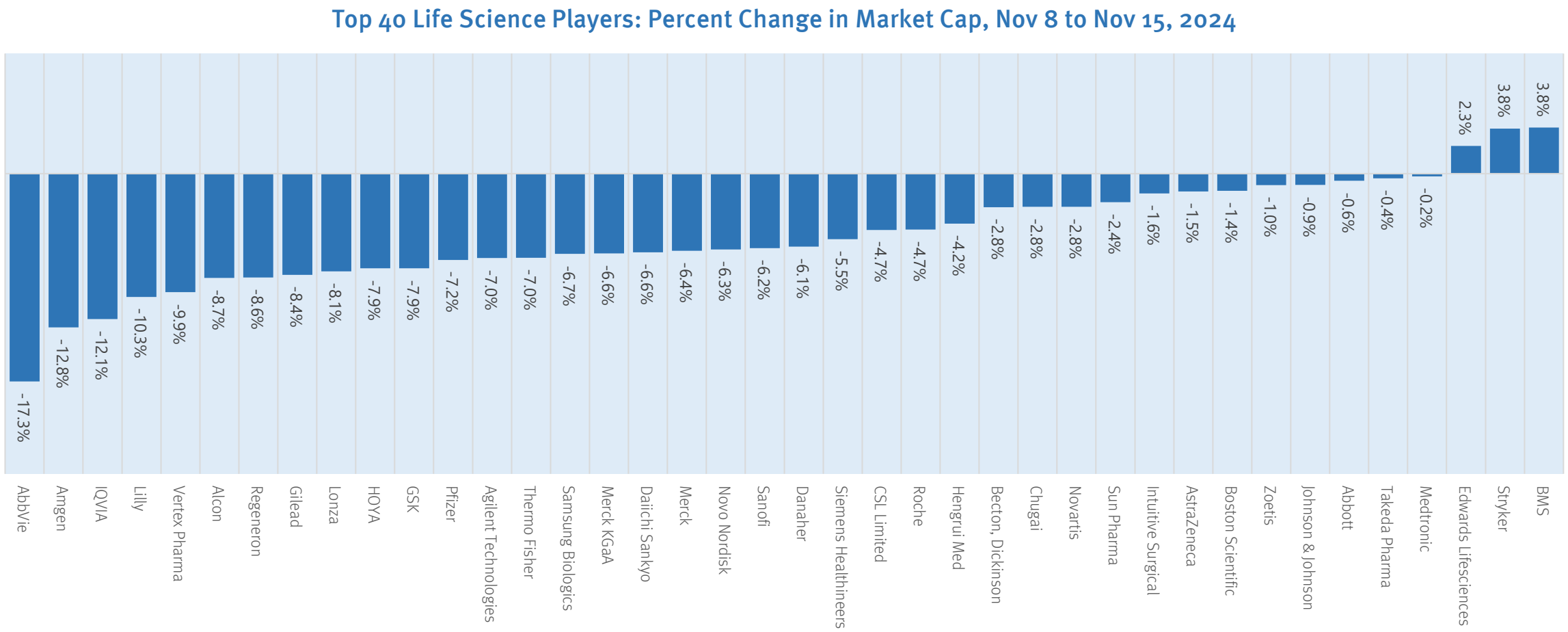


The number of negative EV life sciences companies has risen to 135 from 129 a month ago.

Source: CapitalIQ and Stifel analysis

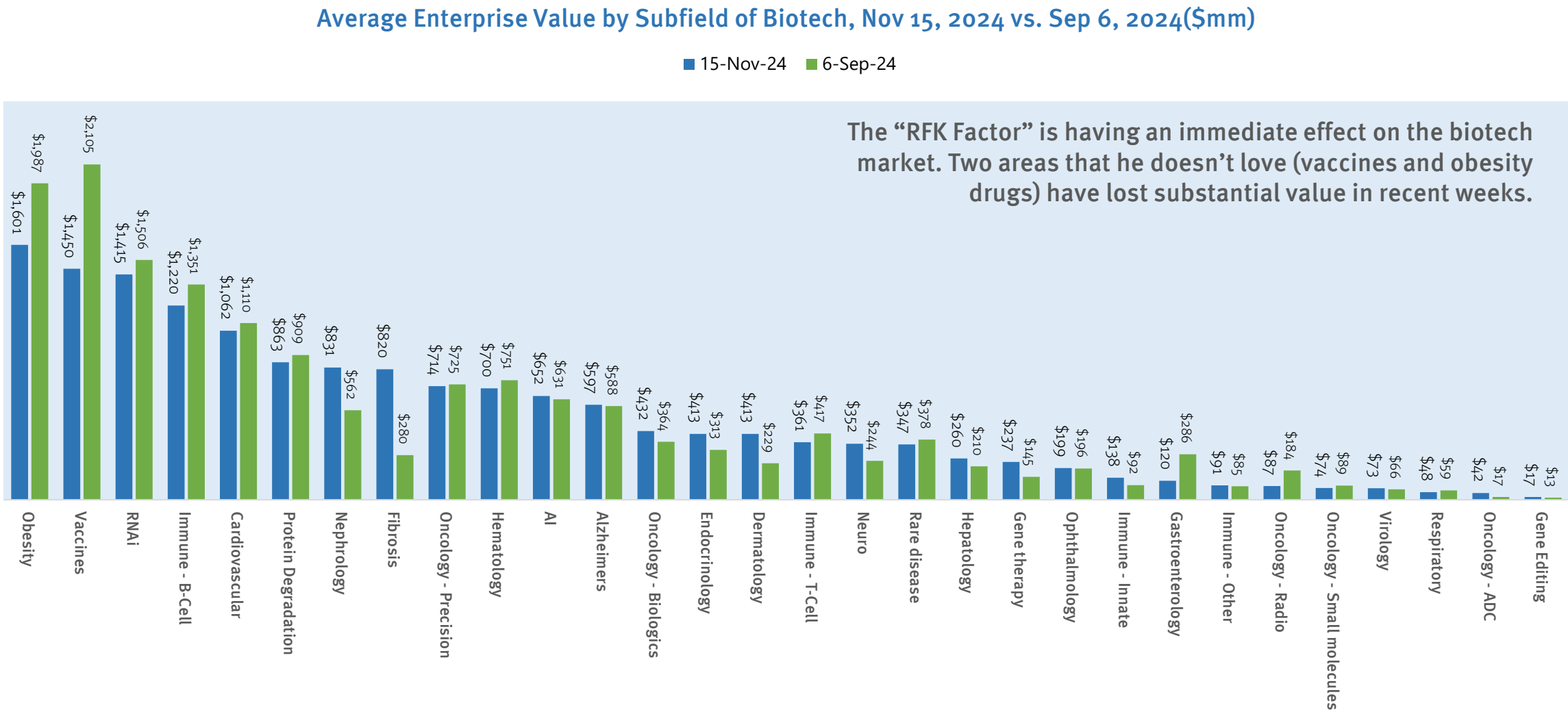
Top 40 Players in Life Sciences: Median Share Price Down 6.1% in Last Week

Last week saw the shares of IQVIA, Amgen and AbbVie take a big spill. Lilly dropped by 10.3% last week (a $73 billion loss).



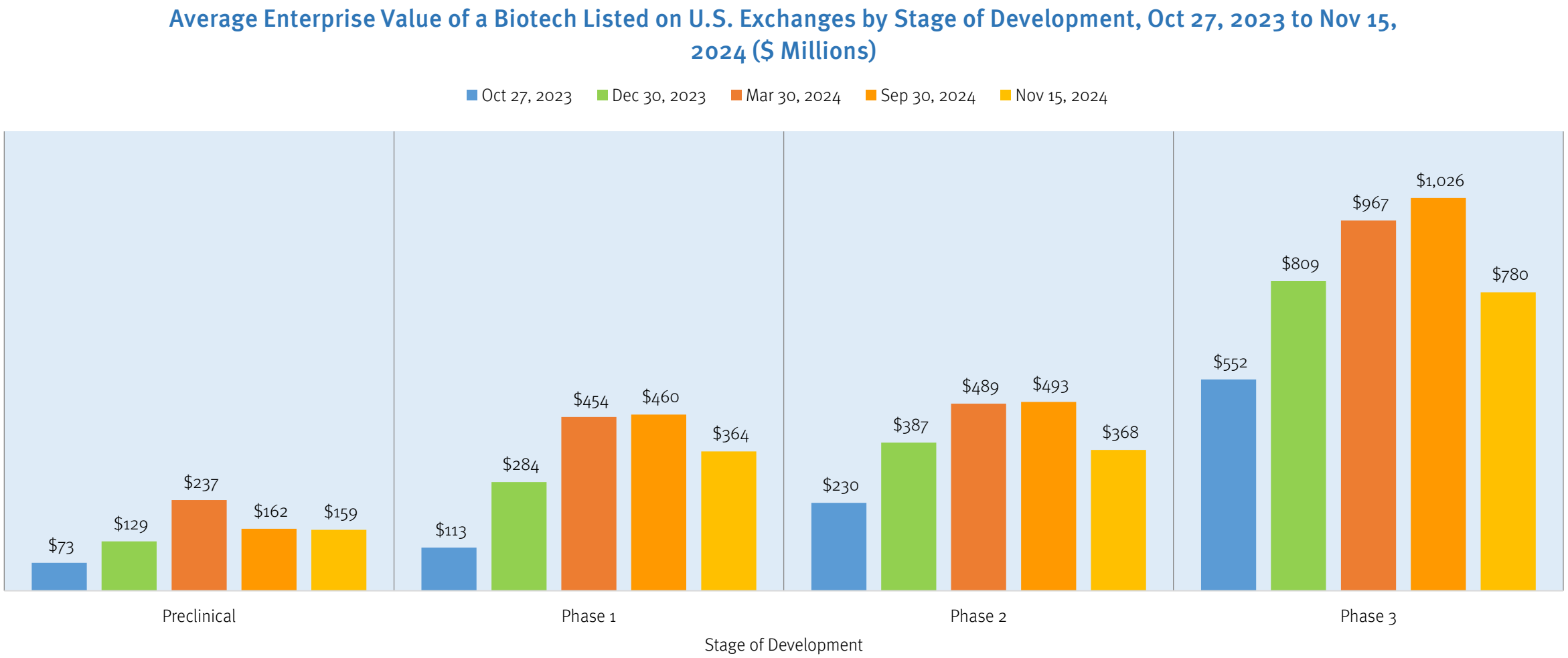
Source: CapitalIQ and Stifel analysis

Vaccines and Obesity Stocks Down. Nephrology, Fibrosis, and Neuro Up. RNA, CV, AI Biotech Stocks Holding Ground



Notes: Data from CapitalIQ. Stifel categorized companies by therapeutic area.

Late Stage Biotechs Getting Hit Hardest in Latest Market Swoon

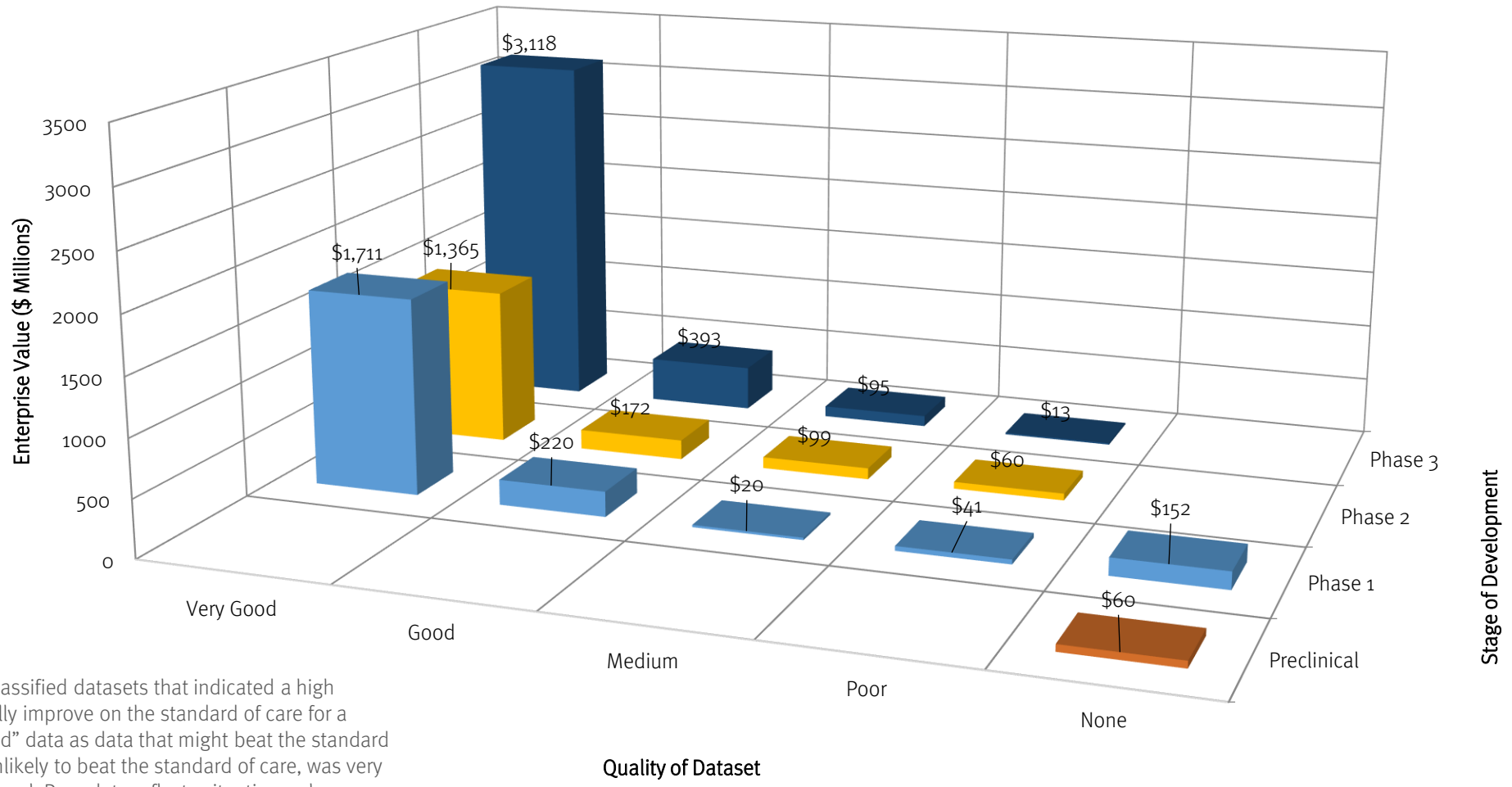


Notes: Data from CapitalIQ. Stifel categorized companies by stage of development.

Strong Quality Premium Remains in the Market

As of last Friday, the ratio of EV of a company with a very good Phase 3 data was 52 times higher than that of a biotech company with no data. This is far higher than the historical norm.

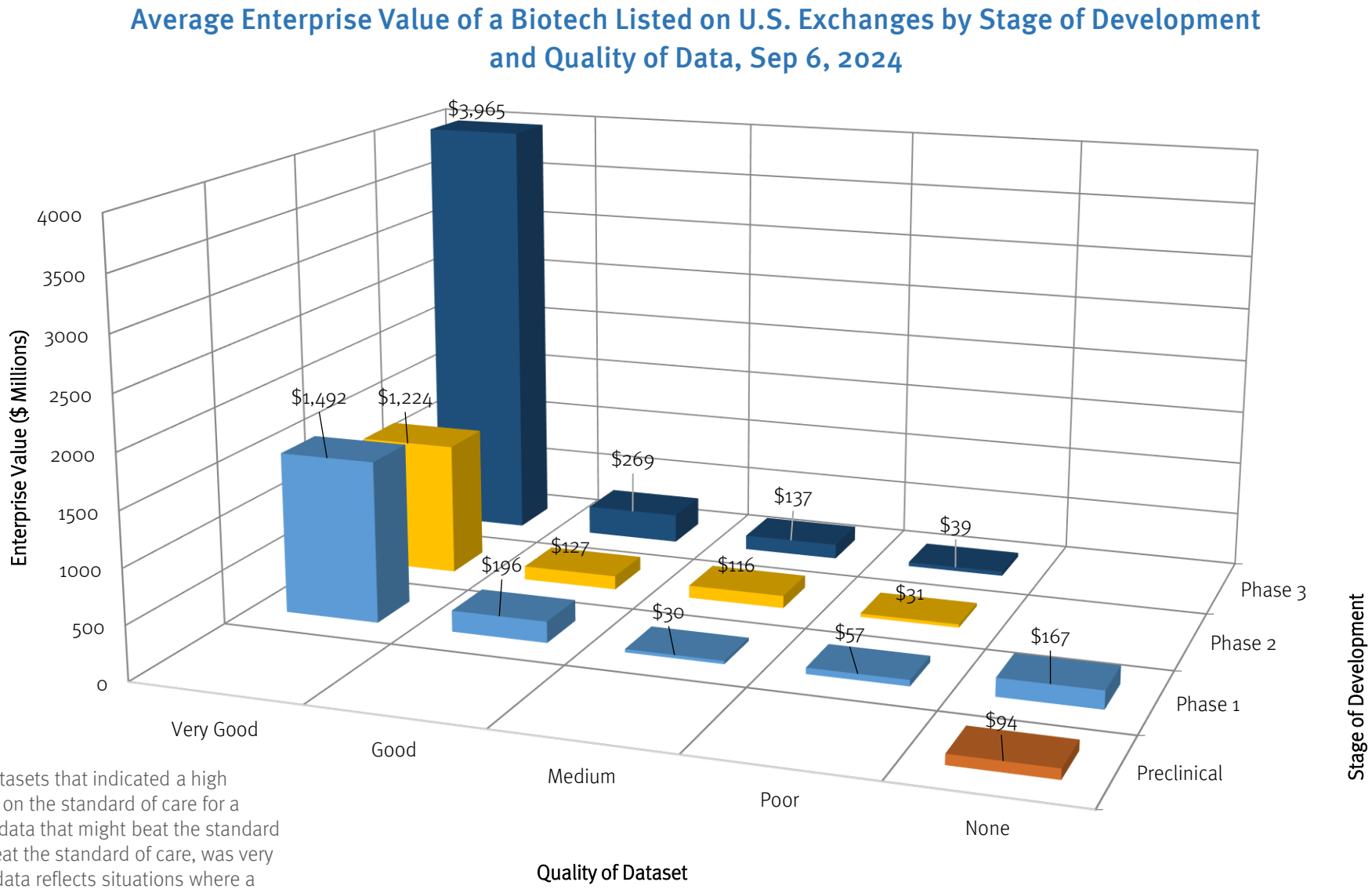
Average Enterprise Value of a Biotech Listed on U.S. Exchanges by Stage of Development and Quality of Data, Nov 15, 2024



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

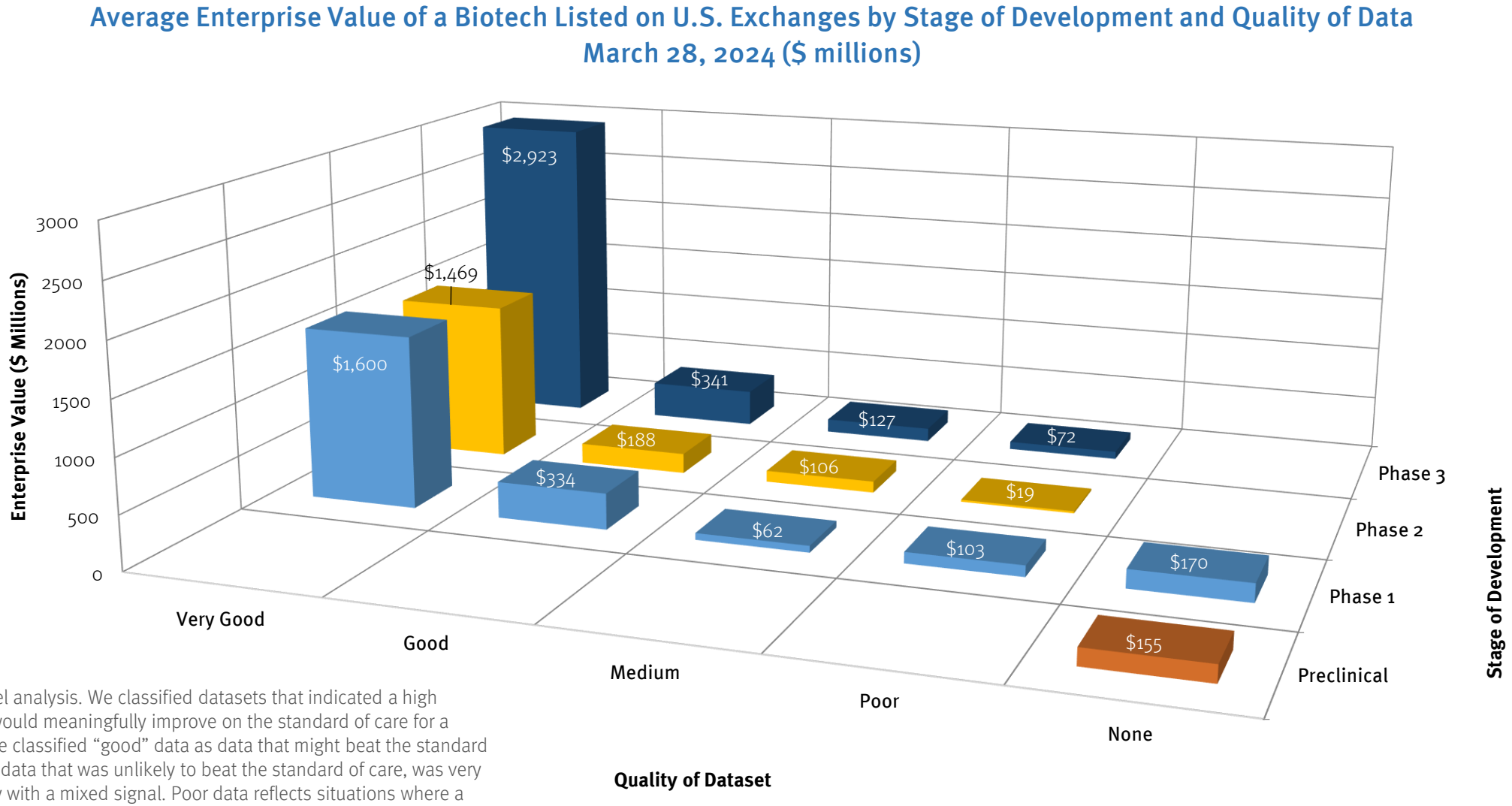
Comparison to Quality Premium Nine Weeks Ago

Nine weeks ago, the ratio of EV of a company with a very good Phase 3 data was 38 times higher than that of a biotech company with no data.



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

For Comparison - Quality x Stage Value Matrix, End of Q1 2024: The Ratio of Biotechs with Very Good Phase 3 Data to No Data Was 15X (vs 52X Today)



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

Biotech Risk Cycles: Assets And Platforms

Bruce Booth of Atlas Venture, *LifeSciVC*, Oct 28, 2024 (excerpt)

Today's market likes products. Platforms aren't in vogue anymore. Investors, especially in the public markets, only want late stage de-risked assets. Pharma only seems to be buying these kinds of asset. VCs need to focus on clinical stage companies. Or so the conventional wisdom goes in the equity capital markets these days.

While it may be the prevailing wind, an innovation ecosystem that allocates capital only to later stage assets risks exhibiting a rather unhealthy blend of investment myopia and historical amnesia. The tone of today's market reveals it's close to suffering those latter conditions.

As context, biotech business models have largely had two flavors for decades: asset-centric investments focused on specific product opportunities and platforms (discovery engines) designed to create new drugs based on novel modalities, technologies, or biological insights. The former is narrower in focus and typically more incremental, the latter broader in aperture often more transformational – but the aspiration of both is to bring new medicines of value to patients. Eventually, if they are successful, even platforms become valued for their later stage assets; despite that convergence on valuation frameworks over time, the corporate journey to get there is very different for these two types of models, as is their impact on the innovation ecosystem. They also face a different set of risks: scientific risks, financial risks, competitive/differentiation risks, binary and idiosyncratic risks, etc…

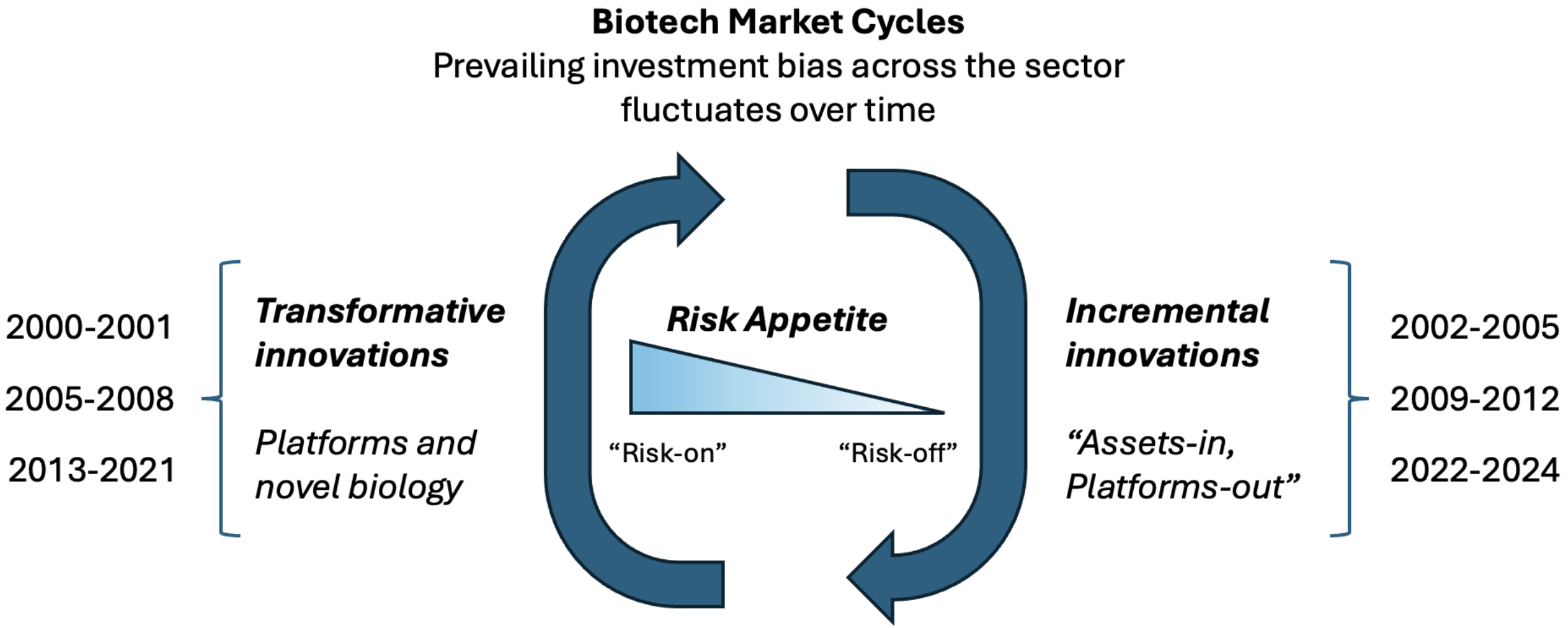
That said, nearer term asset-centric investment opportunities also exist, and offer up attractive returns in different parts of the cycle, especially high cost of capital environments like today. In-licensing molecules from other players, due to a partner's strategic shifts, budget challenges, or geographic access, can be a great way to jumpstart early stage companies around more advanced assets.

The constant cycling of sentiment, and the fluctuating willingness of the market to underwrite innovation risk, is an essential reality in a fluid dynamic market. Spaces get over-bought or over-sold at different stages of the sector. In venture, where the ultra-long-bias of illiquid private investments mean you can't instantly change your portfolio construction, responding violently to changes in the cycle (and what's hot right now) is a recipe for chaos. The resetting of the market in the past two years has been a healthy one for the long term, and hopefully helped elevate themes of capital efficiency and discipline back into the early stage investment model. But there's a point where the pendulum between assets and platforms has swung too far, and we might be reaching it.

For those of us with a few decades under our belts, we know it will swing back: high risk, high innovation deals will be back – hopefully bringing transformative medicines forward for the benefit of patients and investors alike. But it requires a long-term view that embraces the cyclicality of our sector – and the patience to see multiple horizons ahead of us.

Source: https://lifescivc.com/2024/10/biotech-risk-cycles-assets-and-platforms/

Biotech Risk Cycles: Assets And Platforms



Source: https://lifescivc.com/2024/10/biotech-risk-cycles-assets-and-platforms/

Casdin Capital Leads a Strong Month for Biopharma Funds

Steve Taub, *Institutional Investor*, Nov 13, 2024 (excerpt)

Most life sciences and biopharma-focused hedge funds posted solid gains in October in what was otherwise a flat month for the broader market. Even so, most of the funds continue to lag the market.

The group was led by Casdin Capital, which surged 16 percent last month, according to an investor. This puts its share class that invests only in public securities up more than 40 percent for the year. However, the share class remains below its high-water mark. According to a regulatory filing, three names combined accounted for nearly 40 percent of the firm's U.S. stock portfolio at the end of the second quarter: BioLife Solutions, Revolution Medicines, and Sarepta Therapeutics. In October, BioLife was down a bit, Sarepta was up slightly, and Revolution jumped 18 percent, driving overall returns. (Third-quarter holdings reports are due later this week.)

RTW Investments rose 13 percent last month, bringing its gain for the year to 13 percent, according to an investor. But it remains solidly behind the overall market's returns. RTW is more diversified than Casdin, as two stocks each accounted for roughly 8 percent of assets at the end of June: Madrigal Pharmaceuticals and Avidity Biosciences.

Shares of Madrigal had a 22 percent surge in October, most of the increase coming on the final day of the month when the company reported a much smaller third-quarter loss than analysts were expecting. The stock is up an additional 30 percent already this month.

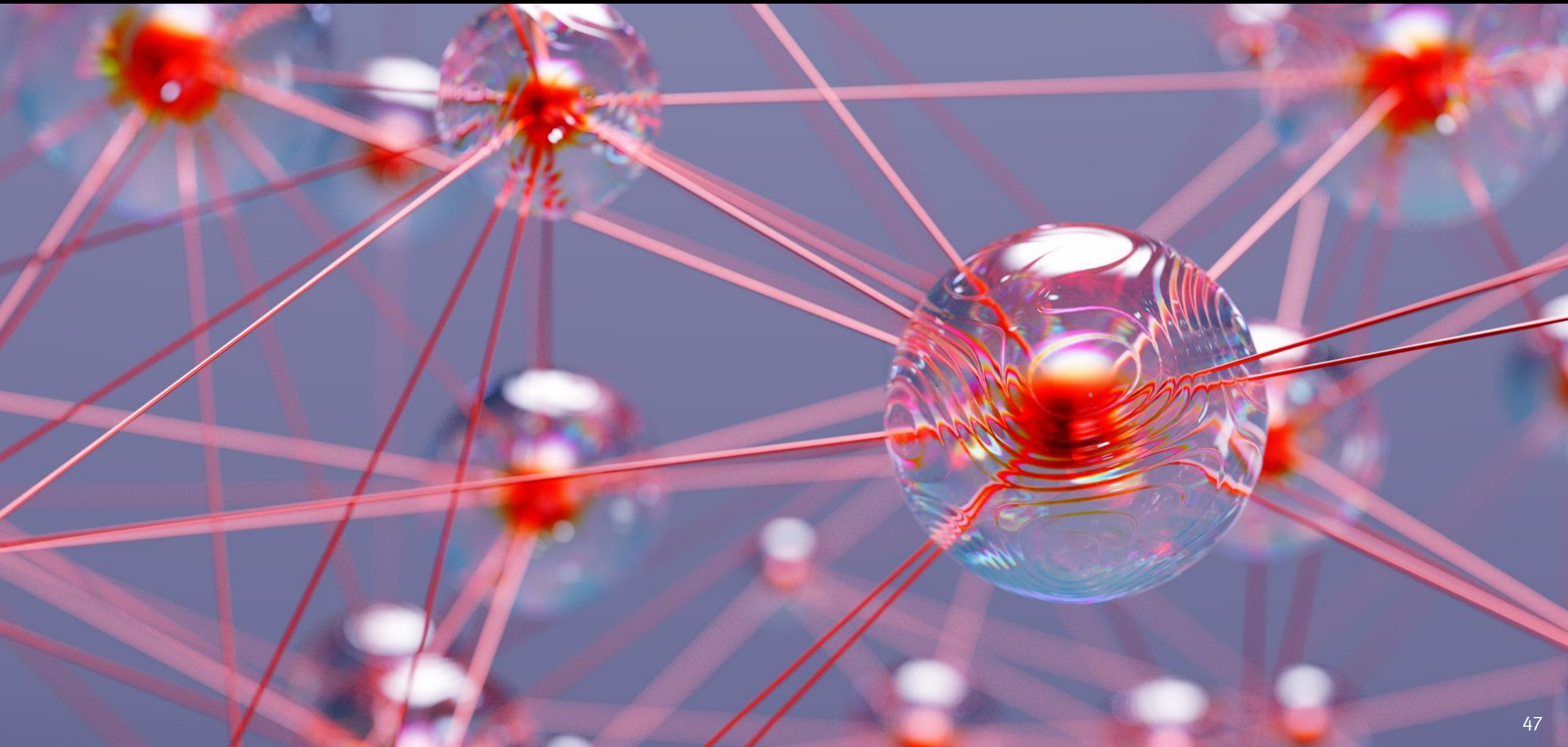
The Janus Henderson Biotech Innovation Fund climbed more than 2 percent, less than many of its peers. But it continues to lead the strategy, up 42.2 percent for the year, according to a hedge fund database.

Elsewhere, RA Capital Management gained 2 percent last month and is up 16.7 percent for the year, an investor says. October's increase was notable given that shares of Ascendis Pharma, the largest long position and responsible for more than 16 percent of capital, fell about 18 percent.

Avoro Capital Advisors was up 1.6 percent for the month, boosting its gain for the year to 14.3 percent, according to an investor. Soleus Capital added 2.1 percent, expanding its 2024 rise to 13.9 percent, said the investor.

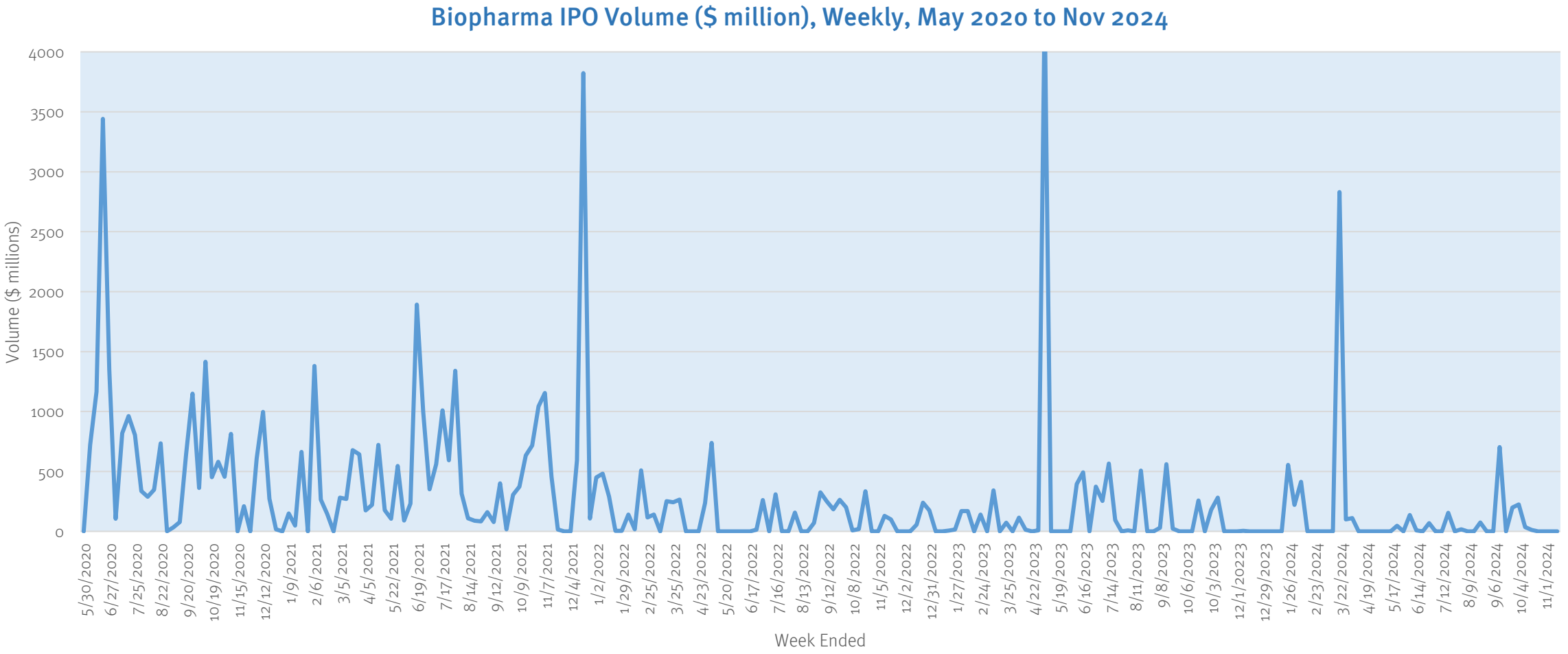
Source: https://www.institutionalinvestor.com/article/2eopheqm3tukhti7vvt34/hedge-funds/casdin-capital-leads-a-strong-month-for-biopharma-funds

Capital Markets Update



No IPO Activity in the Last Two Weeks

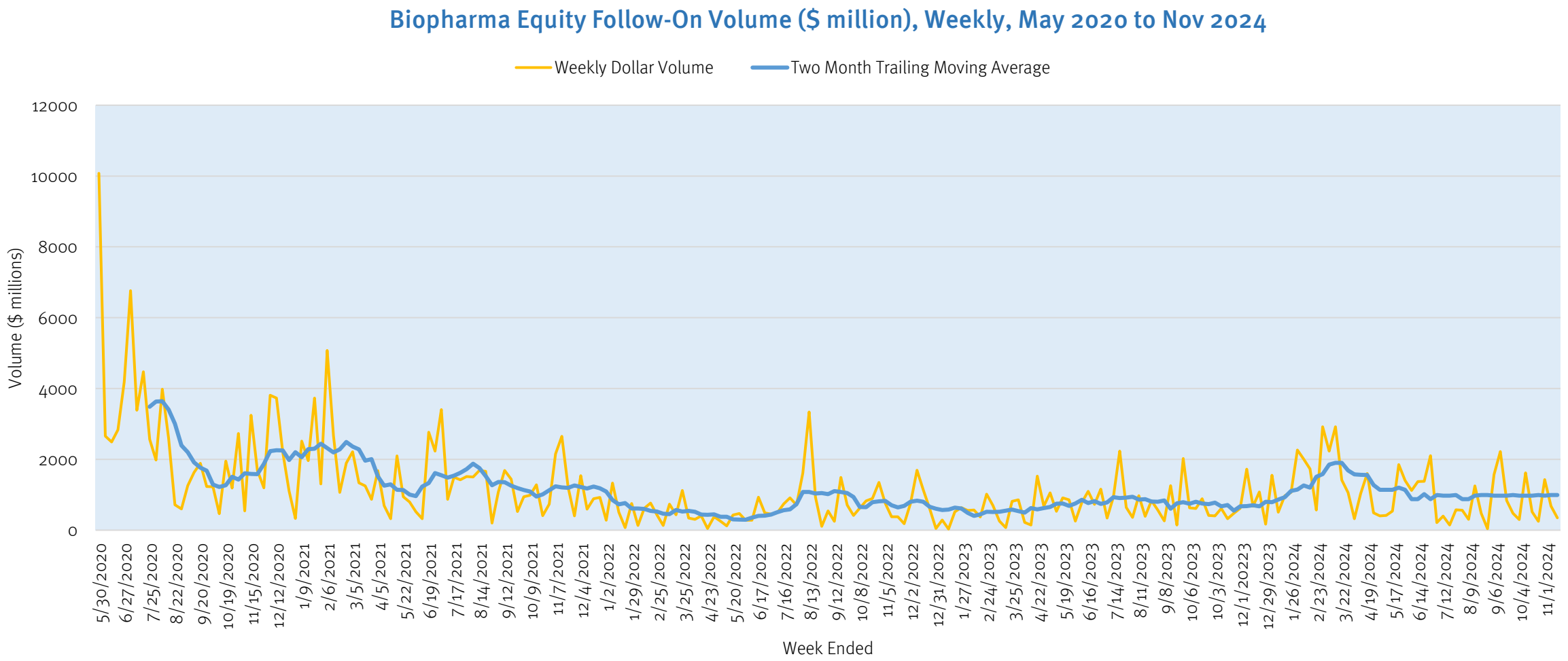
The IPO market came to a halt in the period surrounding the U.S. Presidential election. We expect to see the market pick up once the current volatility in the biotech market clears out.



Source: Data from CapitalIQ.

Equity Follow-On Market Slowing in Recent Weeks

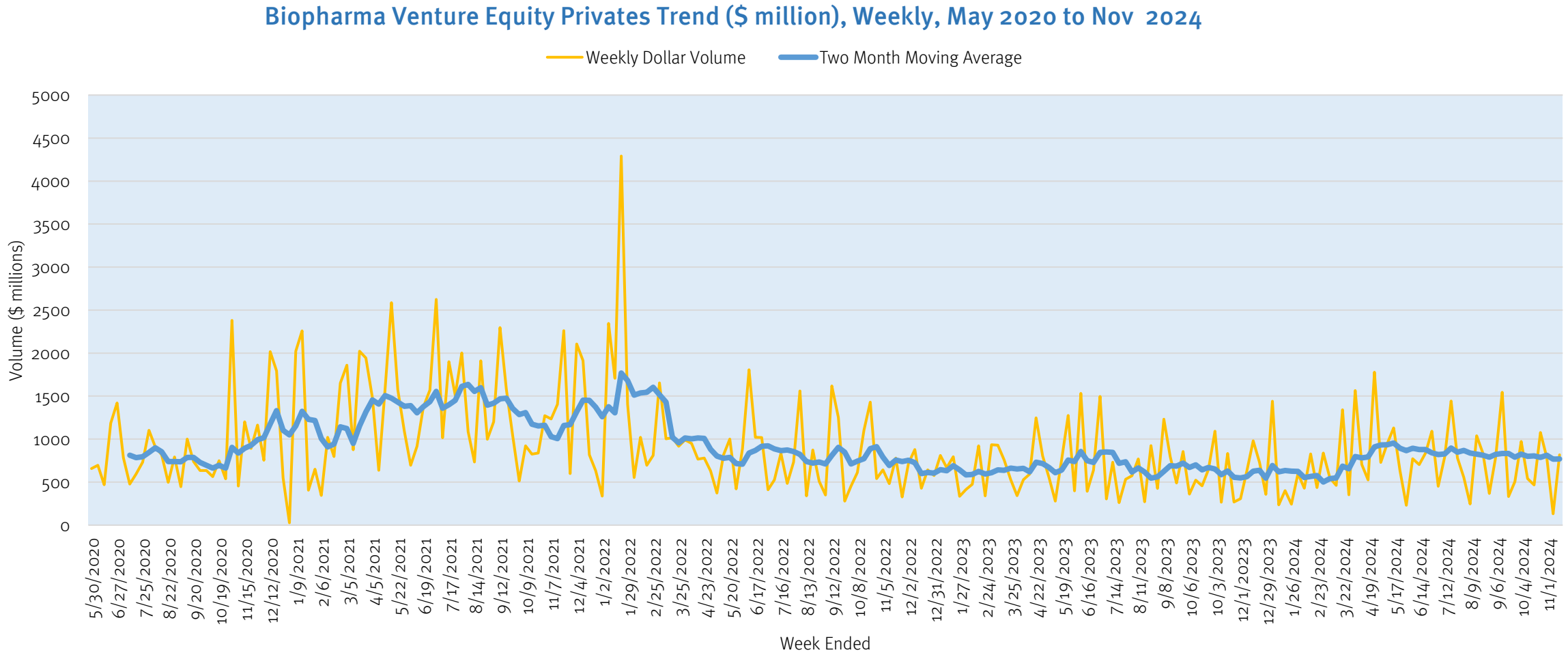
We have seen one billion in equity follow-on's raised in the last two weeks. This is well below the average levels seen earlier in the year.



Source: Data from CapitalIQ.

Private Venture Equity Market Normal in Recent Weeks

Weekly volume of venture privates this year has averaged $750mm. This was very close to the volume last week. We did see exceptionally slow volume the week before when the Presidential election in the U.S. was underway.



Source: Data from CapitalIQ, Crunchbase.

Alentis Therapeutics Raises $181.4 Million in Series D Financing

Basel, Switzerland – Nov 12, 2024: Alentis Therapeutics ("Alentis"), the clinical-stage biotechnology company developing treatments for Claudin-1 positive (CLDN1+) tumors and organ fibrosis, announced today that it has raised $181.4 million in Series D financing, supported by a syndicate of top-tier biotech investors. The financing will support Alentis to develop a deep pipeline of CLDN1 targeted medicines for solid tumors.

The funding round was led by OrbiMed with co-leads Novo Holdings and Jeito Capital. New investors Frazier Life Sciences, Longitude Capital, Catalio Capital, Piper Heartland Healthcare Capital and Avego Bioscience Capital participated in the round. Significant backing was also received from existing investor RA Capital Management, along with support from Morningside Venture Investments, BB Pureos, Bpifrance through its InnoBio 2 fund, as well as other early institutional investors, all of whom have been instrumental to Alentis' development path.

The proceeds of the financing will be used to conduct Phase 1/2 clinical trials of two first-in-class ADCs targeting CLDN1, ALE.P02 and ALE.P03, further development of the pipeline, and general corporate purposes.

The FDA recently cleared an IND application for a Phase 1/2 clinical trial of ALE.P02 (with a tubulin inhibitor) in advanced or metastatic CLDN1+ squamous solid tumors. The clinical trial is expected to commence Q1 2025. For ALE.P03 (with a topoisomerase I inhibitor), a first-in-human trial in patients with CLDN1+ tumors is planned to start in 2025.

"This financing is a testament to the transformational potential of CLDN1 antibody-drug conjugates (ADCs) for the treatment of solid tumors. We're excited to execute our development strategy and deliver clinical data for our programs over the next 12-18 months."

Roberto Iacone
Chief Executive Officer, Alentis Therapeutics

Source: https://alentis.ch/alentis-therapeutics-raises-181-4-million-in-an-oversubscribed-series-d-financing-to-advance-the-clinical-development-of-anti-claudin-1-adcs-in-solid-tumors/

A Small Biotech Fund Gets a Boost From Wall Street Titans

CATALIO
CAPITAL MANAGEMENT

Oliver Barnes and Antoine Gara, *Financial Times*, November 17, 2024 (excerpt)

The list of investors backing little-known life sciences fund Catalio Capital reads like a roll call of private equity and hedge fund titans. Among them: Thoma Bravo's Orlando Bravo, Brevan Howard's Alan Howard, Stanley Druckenmiller and KKR's Henry Kravis.

How a tiny biotech venture capital fund led by 33-year-old managing partner George Petrocheilos attracted such a kaleidoscope of finance luminaries is a story of equal parts hustle, chutzpah and connections.

It has not hurt that the father of Petrocheilos's co-founder Jacob Vogelstein is a famed geneticist who has allowed his son's firm to incubate companies bearing some of his most promising ideas in cancer treatment. Petrocheilos's pater and mitera were also early-stage investors in Catalio, whose name is the Greek word for "catalyse," or speed up.

Regardless of how Catalio amassed capital or marshalled resources, the firm's work is paying off: It has returned more than $300mn to its limited partners in recent years, a rare feat in a tough market.

"This guy will call anybody — that's the beauty about him," Kravis said of Petrocheilos in an interview. "There is no one he won't speak to. It is amazing how many people he has gotten to know over the years who adore him. They have given him money and they continue to give him more money." KKR recently purchased a minority stake in the group, its first investment in an early-stage life sciences investing fund.

Led by its relentlessly networking Greek-born managing partner Petrocheilos and his co-founder Vogelstein, a scientist who met Petrocheilos while studying at Johns Hopkins University, Catalio has engineered 20 exits since it was founded four years ago. Its assets under management have topped $1.3bn, a speedy ascent in a sector that has struggled to attract new capital in recent years.

Vogelstein plays the role of the "quiet and smart" expert "digging into the science of investments", while Petrocheilos is the networker and fundraiser with "more energy than an Energizer bunny," according to Kravis, who serves as Catalio's chair.

Catalio has managed to ride out a choppy few years in the biotech VC industry, in which firms have struggled against rising interest rates and a shortage of capital available to biotechnology companies spending heavily to develop products with uncertain financial prospects.

Source: https://www.ft.com/content/39043ad3-044d-46ce-a72c-a3e58f95be26

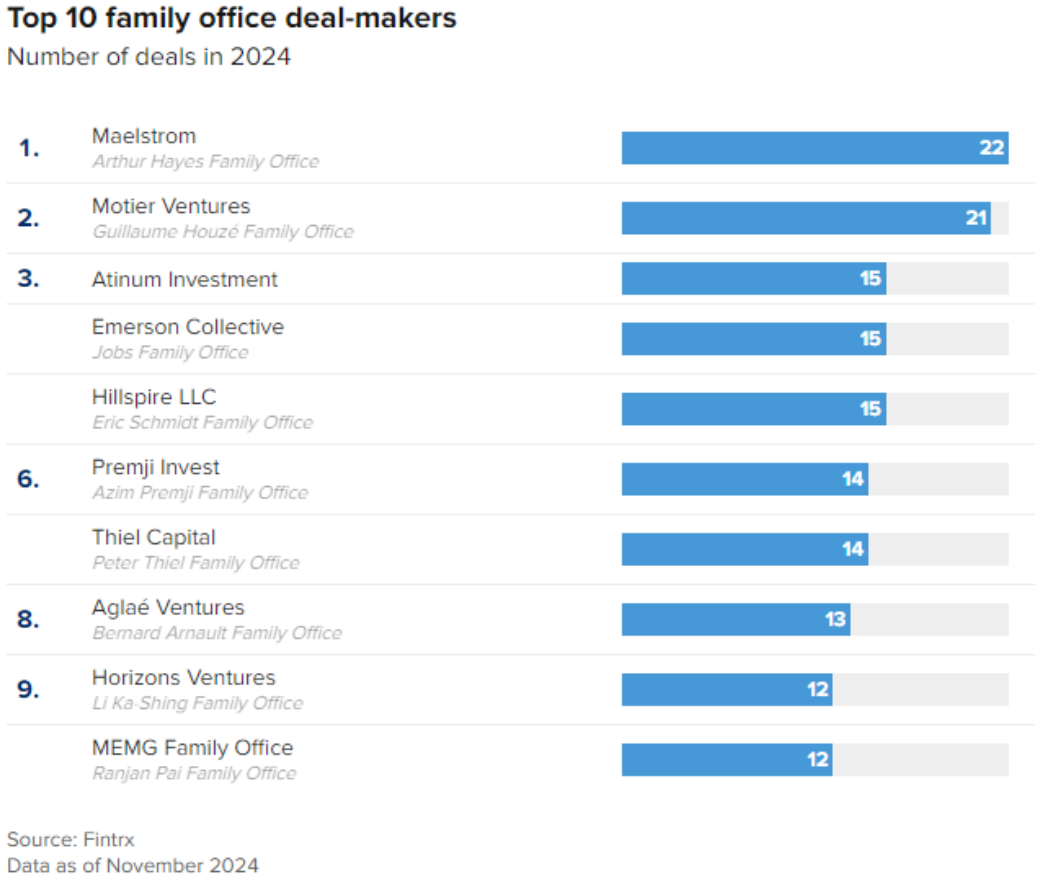
The Top 10 Family Offices for Startup Investments

Robert Frank, *CNBC*, November 15, 2024 (excerpt)

The top 10 family offices for startup investments made over 150 investments combined this year, in everything from biotech and energy to crypto and artificial intelligence, according to a new analysis.

CNBC partnered with Fintrx, the private wealth intelligence platform, to analyze single family offices that made the largest number of investments in private startups in 2024. The list, a first of its kind, sheds light on the investments by some of the biggest names in family offices, from Bernard Arnault's Aglaé Ventures to Laurene Powell Jobs' Emerson Collective and Peter Thiel's Thiel Capital. It also reveals names that are little known outside the secretive world of family offices — the private investment arms of wealthy families — but that have become major players in the world of venture capital and private markets.

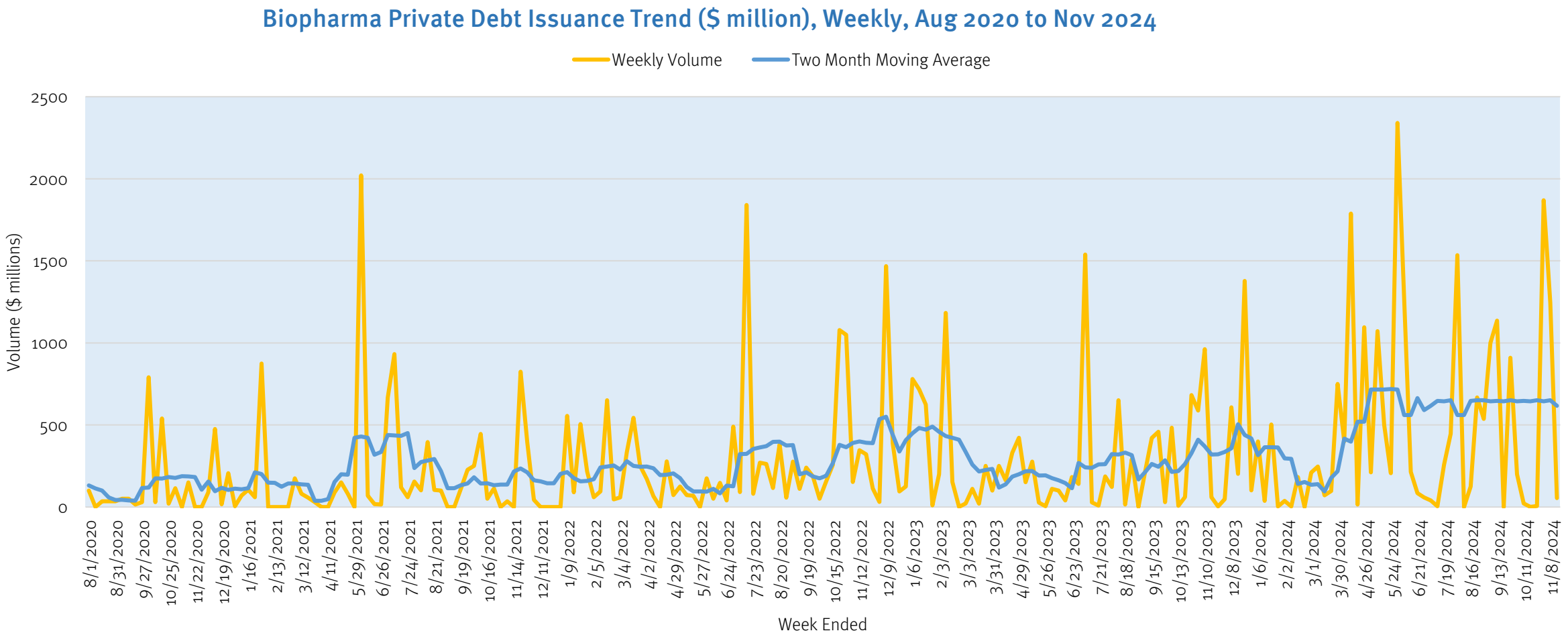
The biggest family offices, such as Hillspire, Thiel or Aglaé, have growing teams of deal and tech experts who can analyze investments and valuations. Smaller family offices and those that don't specialize in tech startups more typically invest through a VC fund. One of the biggest trends in family offices is "co-investing," meaning a VC fund takes the lead on an investment and the family office invests as partners, often with lower fees.



Source: https://www.cnbc.com/2024/11/15/top-10-family-offices-startup-investments.html

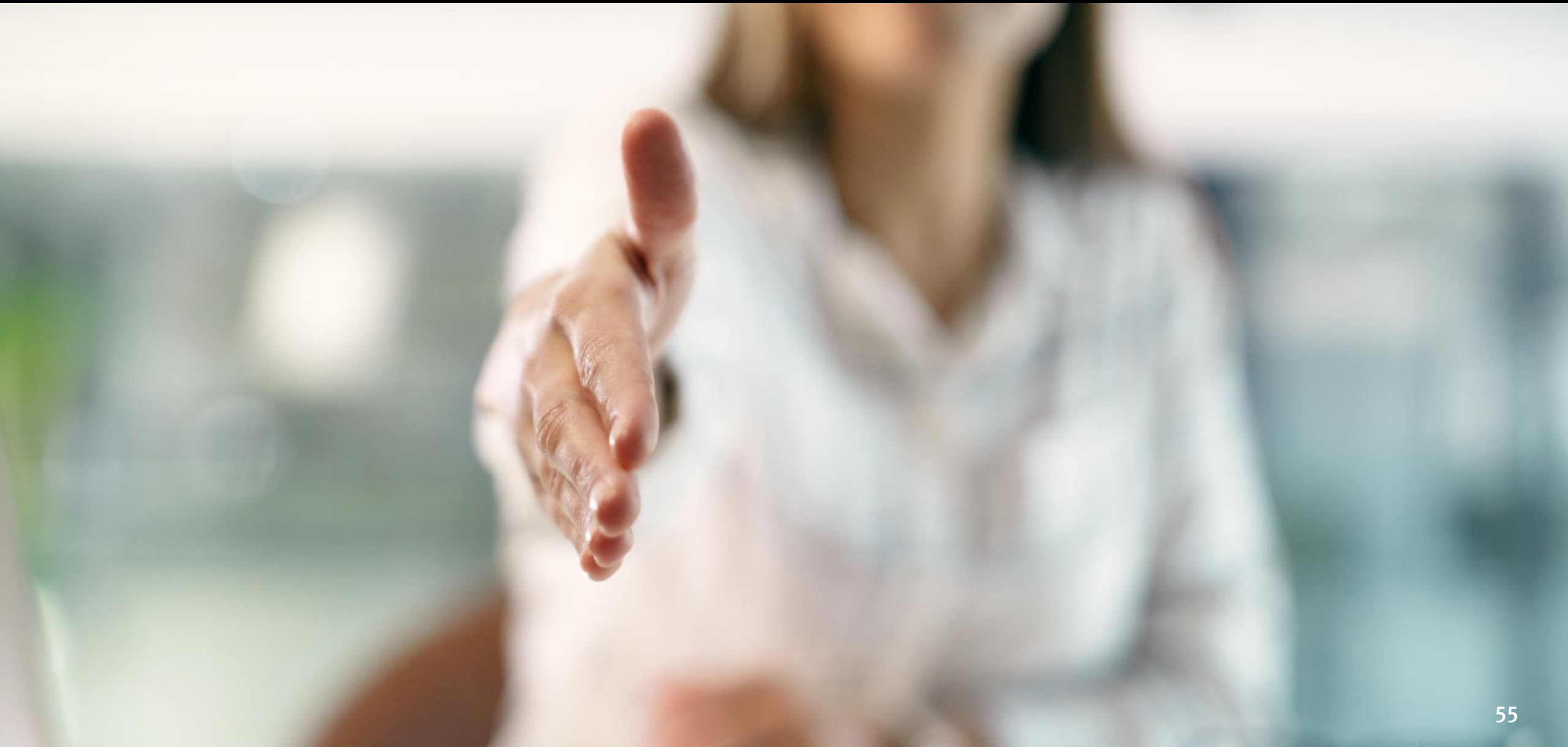
Biopharma Private Debt Market Remains Strong

Volumes in the private debt market have been elevated in the last several months. The issuance volume seen in the last four weeks have been in line with the levels seen since May.



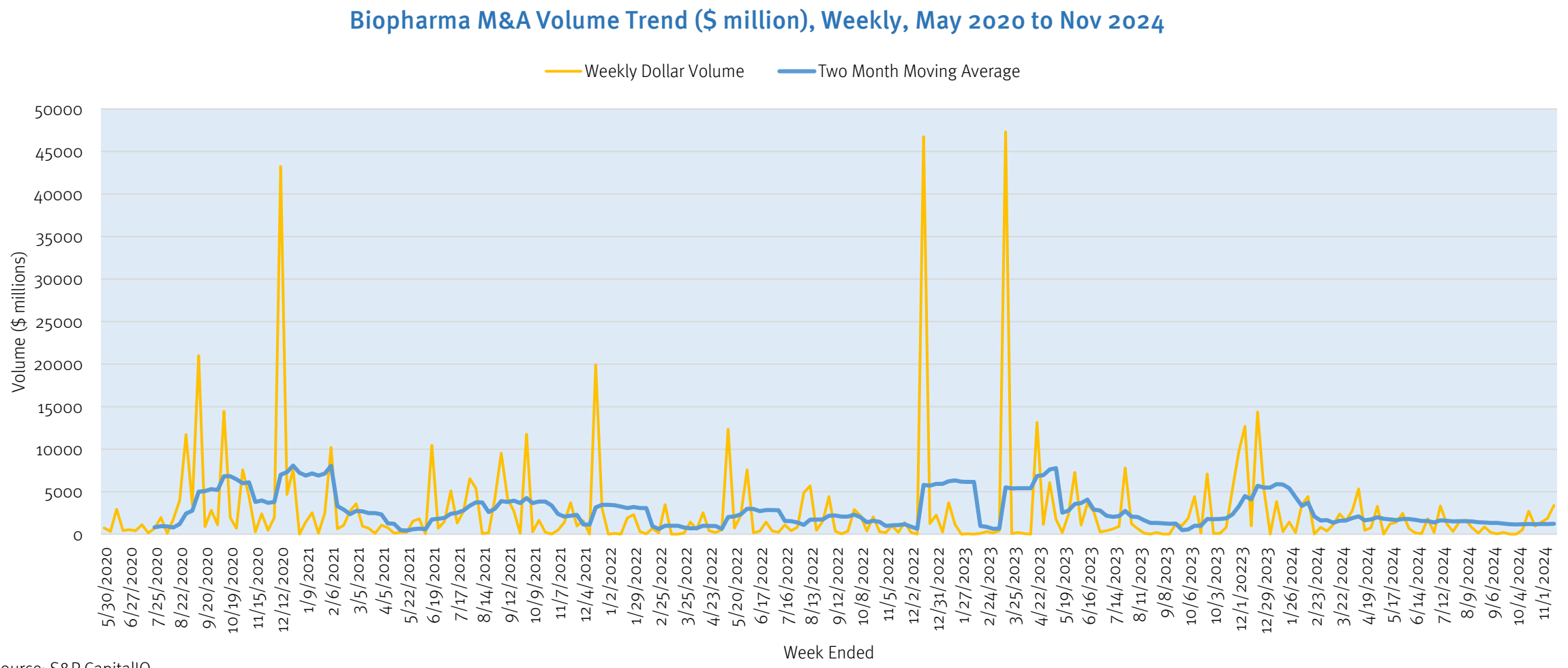
Source: Data from CapitalIQ, Crunchbase, Stifel research.

Deal News



Biopharma M&A Volume in November Has Been Solid

We have seen $5 billion in M&A volume thus far in the month of November. This is on track with the level seen last month and above levels seen throughout the rest of the year. The largest deal last week was BioNTech's $850 million acquisition of Chinese biotech Biotheus. The largest proposed deal was Halozyme's $2.1 billion offer to purchase Evotec.



Source: S&P CapitalIQ

Halozyme Offers $2B for Evotec to Expand Beyond Delivery Tech Used by J&J and Roche

Nick Paul Taylor, *FierceBiotech*, Nov 15, 2024 (Endpoints)

Halozyme Therapeutics has bid to buy Evotec for around 2 billion euros ($2.1 billion). Evotec confirmed it received an offer and said it is analyzing the proposal before deciding on the next steps.

News of the offer arrived days after Bloomberg reported that the private equity group Triton Partners, which has built an almost 10% stake in Evotec, was weighing a move to acquire the drug discovery shop. The flurry of interest follows a year in which Evotec's share price has plummeted. That decline allowed Halozyme to offer a 27.5% premium over Evotec's last close price and still barely break $2 billion.

Halozyme has built a business on Enhanze, the drug delivery technology that enables the subcutaneous administration of products including Johnson & Johnson's Darzalex. The composition of matter patent on Enhanze expires in 2027. Based on co-formulation patents, Halozyme expects to continue to receive royalties on products that use Enhanze for years after 2027. Some royalty streams will dry up by 2030 but Halozyme expects others to continue into the next decade and, in one case, beyond. Even so, the company has begun preparing for life after Enhanze.

Helen Torley, Halozyme's CEO, explained the offer in a statement. Buying Evotec would "diversify and extend Halozyme revenue and EBITDA growth and durability well into the next decade and beyond," Torley said. Evotec's drug discovery platform would become a center of excellence, Halozyme said, and its manufacturing platform would complement Enhanze.

Evotec Headquarters

Source: https://www.fiercebiotech.com/biotech/halozyme-offers-2b-evotec-expand-beyond-delivery-tech-used-jj-and-roche

BioNTech to Acquire Biotheus to Boost Oncology Strategy

Press Release, Nov 13, 2024

BioNTech SE and Biotheus today announced the signing of a definitive agreement for the acquisition of Biotheus, a clinical-stage biotechnology company dedicated to the discovery and development of novel antibodies to address unmet medical needs of patients with oncological or inflammatory diseases. With the acquisition, BioNTech will obtain full global rights to the late-stage clinical asset BNT327/PM8002, an investigational bispecific antibody targeting PD-L1 and VEGF-A. The transaction is part of BioNTech's oncology strategy, aimed at enhancing the company's capabilities to research, develop and commercialize combination therapies using BNT327/PM8002. Clinical trials with BNT327/PM8002 and the PD-(L)1 x VEGF bispecific class of drugs have demonstrated encouraging clinical activity in various tumor types including in patients with PD-L1-low and -negative tumors who have typically been less responsive to current checkpoint inhibitor treatments.

"The acquisition of Biotheus builds on our successful ongoing collaboration on BNT327/PM8002 and other investigational bispecific antibodies," said Prof. Ugur Sahin, M.D., Ph.D., CEO and co-founder of BioNTech. "We believe that BNT327/PM8002 has the potential to set a new standard of care in multiple oncology indications, surpassing traditional checkpoint inhibitors. We are committed to advancing its research and development in combination with our investigational mRNA vaccines, targeted therapies, and immunomodulators with the aim of enhancing outcomes for patients with solid tumors." "We are thrilled to deepen our bond with BioNTech. We share the goal of advancing the development of BNT327/PM8002 for future combination therapies in the fight against cancer," said Xiaolin Liu, President, CEO, and Co-Founder of Biotheus. "We believe that BNT327/PM8002 holds significant potential across various tumor indications, and we have an exciting pipeline of innovative investigational assets under development including an antibody discovery and development platform. As we move forward, we are committed to leveraging our strengths with the aim of advancing transformative cancer treatments and enhance our ability to develop treatments for patients in need."

BNT327/PM8002 has shown encouraging efficacy and tolerability in patients across various tumor types, with more than 700 patients treated in clinical trials to date. Multiple registrational trials are planned to start in 2024 and 2025, evaluating BNT327/PM8002 plus chemotherapy in various solid tumor indications including in patients with small cell lung cancer, non-small cell lung cancer and triple-negative breast cancer

Under the terms of the agreement, BioNTech will pay Biotheus shareholders an upfront consideration of $800 million, predominantly in cash, with a small portion in American depositary shares ("ADS"), to acquire 100 percent of the issued share capital, subject to customary purchase price adjustments, plus additional performance-based contingent payments of up to $150 million if certain milestones are met. Upon closing, BioNTech will gain full rights to Biotheus' pipeline candidates and its in-house bispecific antibody drug conjugate capability. The acquisition will expand BioNTech's footprint in China, adding a local research and development hub to conduct clinical trials. In addition, BioNTech will gain a state-of-the-art biologics manufacturing facility to contribute to its future global manufacturing and supply, and more than 300 Biotheus employees in R&D, manufacturing and enabling functions are expected to join the BioNTech workforce.

Source: https://investors.biontech.de/news-releases/news-release-details/biontech-acquire-biotheus-boost-oncology-strategy

Merck Enters into Exclusive Global License for LM-299, An Investigational Anti-PD-1/VEGF Bispecific Antibody from LaNova Medicines for $588 Million Upfront

Merck Press Release, Nov 14, 2024

Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and LaNova Medicines Ltd. (LaNova), a privately held clinical-stage biotechnology company, today announced that Merck has entered into an exclusive global license to develop, manufacture and commercialize LM-299, a novel investigational PD-1/VEGF bispecific antibody from LaNova.

“At Merck, we continue to assemble a strong and diversified oncology pipeline spanning differentiated mechanisms and multiple modalities,” said Dr. Dean Y. Li, president, Merck Research Laboratories. “This agreement adds to Merck’s growing oncology pipeline and we look forward to advancing LM-299 with speed and rigor for patients in need.”

Under the agreement, LaNova has granted Merck an exclusive global license to develop, manufacture and commercialize LM-299. LaNova will receive an upfront payment of $588 million. LaNova is also eligible to receive up to $2.7 billion in milestone payments associated with the technology transfer, development, regulatory approval and commercialization of LM-299 across multiple indications.

LM-299 is an investigational bispecific antibody targeting both programmed cell death protein-1 (PD-1) and vascular endothelial growth factor (VEGF). This innovative therapeutic approach is designed to inhibit both PD-1/PD-L1 and VEGF/VEGFR receptor signaling pathways releasing a key immune checkpoint while also inhibiting the production of new blood vessels (angiogenesis). LM-299 has a differentiated molecular design, comprising an anti-VEGF antibody linked to two C-terminal single domain anti-PD-1 antibodies. A Phase 1 clinical trial for LM-299 is currently enrolling patients in China.

Source: https://www.merck.com/news/merck-enters-into-exclusive-global-license-for-lm-299-an-investigational-anti-pd-1-vegf-bispecific-antibody-from-lanova-medicines-ltd/

“This agreement with Merck is a strong testament to the hard work of LaNova’s talented team of scientists who created LM-299. Through internal R&D innovation and strategic external partnerships, LaNova is committed to advancing its pipeline to benefit patients worldwide.”

Crystal Qin
Chief Executive Officer
LaNova Medicines

Merck and BiotNTech Moves Highlight Importance of Emerging VEGF x PD1 Drug Class

Frank Vinluan, *MedCity News*, Nov 14, 2024 (excerpt)

Cancer drug dealmaking is heating up around promising candidates with the potential to top Merck by going after two targets versus the one addressed by the pharmaceutical giant's blockbuster immunotherapy, Keytruda. Now Merck is joining in with a $588 million deal of its own.

Keytruda is a monoclonal antibody designed to block PD-1, a checkpoint protein on immune cells. LaNova's LM-299 is a bispecific antibody that blocks both PD-1 as well as VEGF, a protein that stimulates growth of blood vessels that support cancer growth. The promise of pairing of both of these mechanisms in a single drug shot to prominence in September with Summit Therapeutics' report of data showing its bispecific drug, ivonescimab, topped Keytruda in a head-to-head clinical trial. In that China-only study, ivonescimab led to a 49% reduction in the risk of disease progression or death compared to Keytruda. This study was conducted by Summit's partner, Akeso. Ivonescimab is already approved in China as a treatment for advanced cases of non-small cell lung cancer.

Interest in bispecifics that target both PD-1 and VEGF drugs is growing. Crescent Biopharma's bispecific candidate addressing those two targets is preclinical, but the company is piggybacking on the industry and investor attention to the drug class, recently striking a deal to go public in a reverse merger.

On Wednesday, BioNTech announced it is paying $800 million up front to acquire partner Biotheus and its PD-L1/VEGF bispecific antibody, BNT327/PM8002. Last year, the German company secured global rights to the molecule outside of Greater China for $55 million up front. In addition to securing rights to the drug itself, the new deal enables BioNTech to expand its footprint with the addition of R&D and biologics manufacturing capabilities in China. BNT327/PM8002 has reached mid-stage studies in advanced cases of breast and lung cancers. The bispecific antibody is also in Phase 1/2 testing in combination with an antibody drug conjugate from BioNTech's partnership with Duality Bio.

Merck has not disclosed its clinical trial plans for LM-299. In a prepared statement, Dean Li, president of Merck Research Laboratories, said the company is continuing to assemble an oncology pipeline spanning differentiated mechanisms and multiple modalities. Merck expects to close the acquisition of the LaNova drug by the end of this year.

Source: https://medcitynews.com/2024/11/merck-acquisition-cancer-bispecific-antibody-lanova-pd1-vegf-mrk/

BiotNTech Sees New Bispecifics as Expanding IO Therapy

Next-generation Bispecific Can Potentially Expand the Reach of IO Therapy

PD-(L)1 monotherapy approved in front line	PD-(L)1 approved as combination therapy or in later line	PD-(L)1 not currently approved
NSCLC PD-L1 ≥ 50%	NSCLC PD-L1 <50% ●	
	TNBC PD-L1 ≥ 10%	TNBC PD-L1 <10% ●
	SCLC	EGFRmut NSCLC ●
HNSCC PD-L1 ≥1%	HNSCC PD-L1 <1%	HR+ HER2- BC
Melanoma	Endometrial Cancer ●	CRC (MSS) ●
MSI-H or dMMR solid tumors	Cervical Cancer ●	Glioblastoma ●
	HCC ●	Ovarian Cancer ●
	Gastric or GEJ Cancer PD-L1 ≥ 1% ●	Gastric or GEJ Cancer PD-L1< 1% ●
		PDAC

● Anti-VEGF approved indications

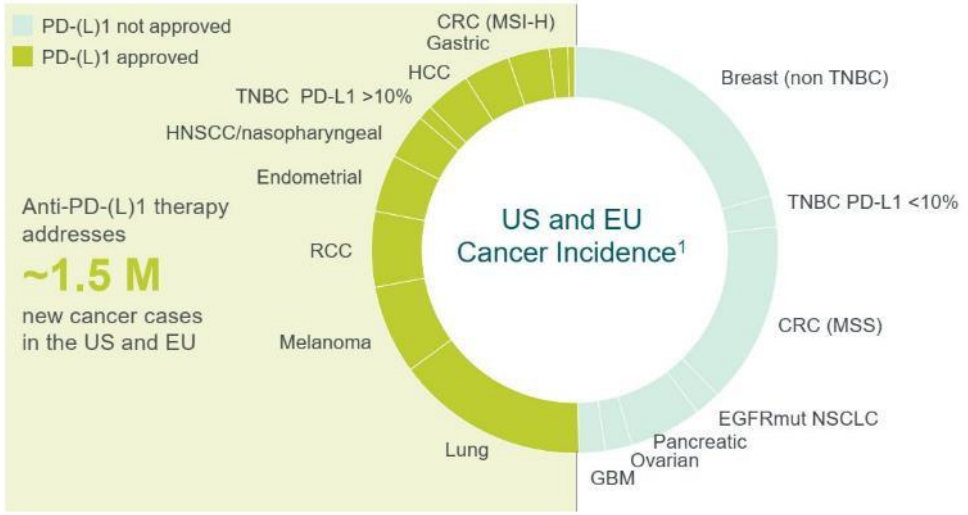
Only selected indications listed

Next-gen PD-(L)1xVEGF bispecific opportunity

Seek improved efficacy profile vs. existing IO | Explore indications non-responsive to current IO

Source: Keytruda Label; Opdivo Label; Tecentriq Label; Imfinzi Label; Libtayo Label; Bavencio Label; Jemperli Label; Loqtorzi Label; Zynyz Label; Avastin Label; Cyramza Label; Lenvima Label; Votrient Label . Selected indications listed based on FDA approval.

Anti-PD-(L)1 Therapy Only Addresses a Fraction of Cancer Incidence



1. US incidence source: NIH and American Cancer Society data EU incidence source: European Cancer Information System, Indications listed on the previous slide are shown.

Eyenovia Halts Phase 3 Myopia Trial. To Consider Strategic Options

Katherine Lewin, *Endpoints News*, Nov 15, 2024 (excerpt)

Eyenovia stopped a Phase 3 trial following a review of the data that found its experimental myopia treatment wasn't going to hit the study's primary endpoint.

The ophthalmic company is now considering strategic options. Its stock $EYEN was down about 73% on Friday morning following the announcement.

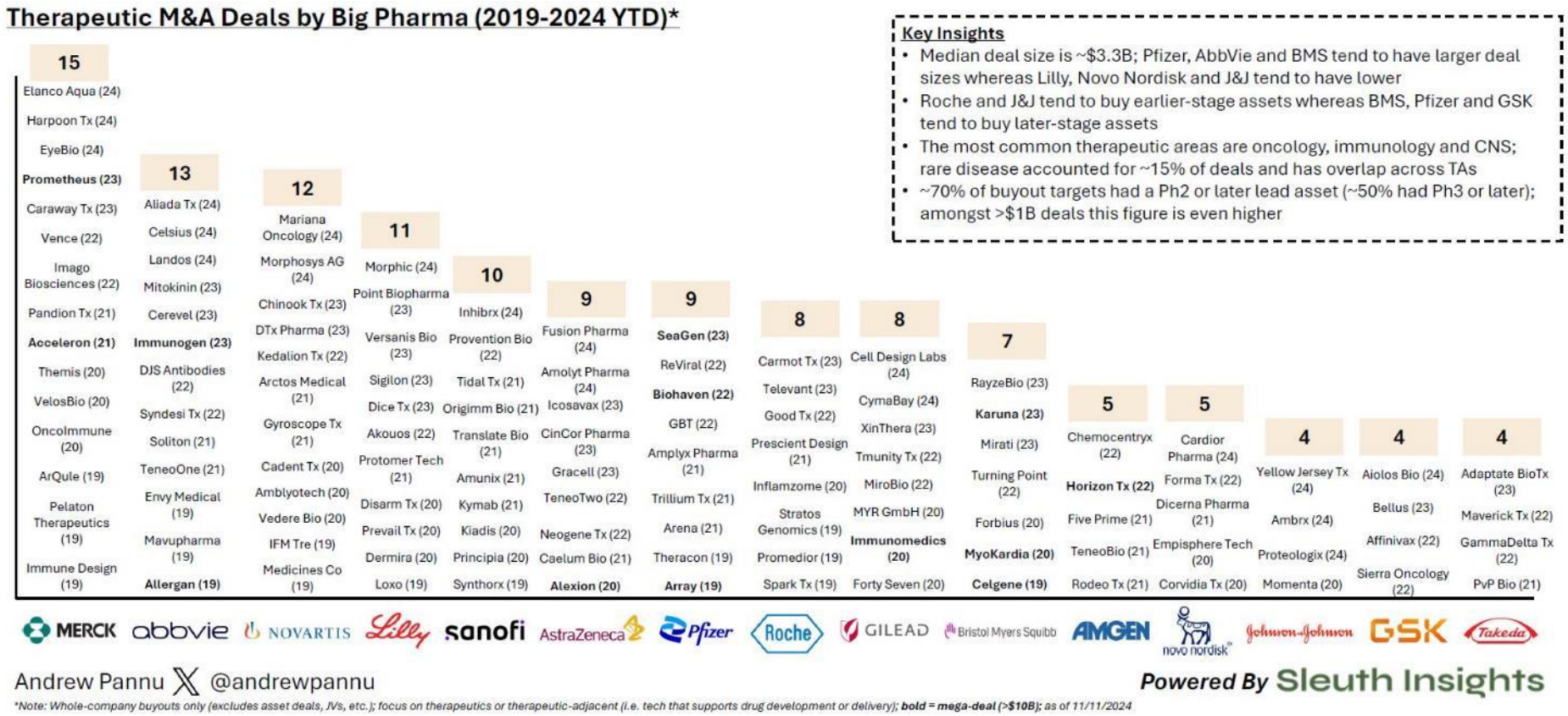
Eyenovia had been investigating a drug-device combination that dispensed atropine as a treatment for pediatric progressive myopia, a form of nearsightedness that grows worse over time due to abnormal eye growth.

According to an independent data review committee, the trial wasn't on target to meet its primary endpoint of a less than 0.5 diopter progression in visual acuity over three years. Diopter progression is the rate used to measure glasses or contact lens prescriptions for people with myopia. The difference between the patients on placebo or atropine was not "significantly different," the company said."

We plan to terminate the study, review the data more thoroughly, and evaluate next steps," Eyenovia CEO Michael Rowe said in a statement.

Source: https://endpts.com/eyenovias-stock-falls-after-it-halts-late-stage-myopia-trial/

Andrew Pannu Studies Big Pharma M&A



1. M&A tends to pick up as company's approach big LOEs, and so unsurprisingly, Merck and AbbVie led the way.

2. For Merck, they're facing a $30B LOE in 2028 with Keytruda - big bets on Acceleron ($11.5B) and Prometheus ($10.8B) + several mid-sized deals are attempts to plug that. They've indicated they're still in the market for more deals, so this probably doesn't slow down either.

3. AbbVie is a few years ahead, having just gone through this process with the $21B Humira LOE in 2023.

4. Every management team has their own style with the types of buyouts they prefer. Pfizer, AbbVie and BMS tend to take big bets, with much higher average deal sizes. In contrast, Lilly, Novo Nordisk and J&J tend to be much lower.

Source: https://x.com/andrewpannu

Industry News

AbbVie Misses in Emraclidine for Schizophrenia

AbbVie Press Release, November 13, 2024 (excerpt)

AbbVie (NYSE: ABBV) today announced that its two Phase 2 EMPOWER trials investigating emraclidine as a once-daily, oral monotherapy treatment for adults with schizophrenia who are experiencing an acute exacerbation of psychotic symptoms, did not meet their primary endpoint of showing a statistically significant reduction (improvement) in the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score compared to the placebo group at week 6.

"While we are disappointed with the results, we are continuing to analyze the data to determine next steps," said Roopal Thakkar, M.D., executive vice president, research and development, chief scientific officer, AbbVie. "We would like to extend our gratitude to the study participants and their loved ones as well as to our network of clinical investigative sites for their participation in these trials. We are confident that our innovative pipeline will continue to bring meaningful therapies to patients, and we remain committed to finding better treatments for people living with psychiatric and neurological disorders."

Change from Baseline to Week 6 in PANSS Total Score

	EMPOWER-1			EMPOWER-2		
	Placebo (N= 127)	**Emraclidine 10mg QD (N = 125)**	**Emraclidine 30mg QD (N = 127)**	**Placebo (N = 128)**	**Emraclidine 15mg QD (N = 122)**	**Emraclidine 30mg QD (N = 123)**
Baseline (SD)	98.3 (8.16)	97.6 (7.65)	97.9 (7.89)	97.4 (8.22)	98.0 (8.49)	97.2 (7.75)
LS Mean (95% CI)	-13.5 (-17.0, -10.0)	-14.7 (-18.1, -11.2)	-16.5 (-20.0, -13.1)	-16.1 (-19.4, -12.8)	-18.5 (-22.0, -15.0)	-14.2 (-17.6, -10.8)

We are quite surprised to see this result given the strength of Cerevel's Phase 1b results. We'd note that the patients in the Phase 1b study were less sick than those in this study. The other big difference between the Phase 1b and the Phase 2 is that the placebo patients responded quite strongly in Phase 2, whereas they did not in Phase 1. This, of course, is not the first time that a high placebo response rate has confounded a clinical trial in schizophrenia and there is good reason (see next page) to think this problem may be controllable. This result obviously has implications for Neurocrine and highlights the risks of doing M&A at high prices based on Phase 1b data. We will be watching BMS's KarXT launch carefully and hoping for success from other companies pursuing novel MOA's such as Merck and Eumentis with the PDE10A approach.

Sources: https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia, https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01990-0

Myths and Realities of PLACEBO RESPONSE:

A 21st Century Prescription

Mark Opler
Clinical Researcher
June 2017

One important indicator of clinical research quality is the extent to which trials detect effect signals (i.e., do trials separate experimental treatments from placebo). Rates of placebo response across multiple therapeutic areas are now historically high and progressively increasing. Multiple reviews in different therapeutic areas, including pain, epilepsy, Crohn's disease, dermatology, schizophrenia, pediatric studies, and others suggest a very distressing trend in that, year over year, the rates of placebo response are going up. One meta-analysis shows how this affects the course of a specific development program.4 In evaluating the efficacy of pregabalin versus placebo in peripheral neuropathy, the results indicate very clearly that the effect of placebo across different indications correlates positively with the year of study initiation. Another intriguing finding from the same meta-analysis revealed an increase in placebo response despite no attendant improvement in the efficacy of pregabalin for studies conducted after U.S. Food and Drug Administration approval. All of this points to a population-level phenomenon in clinical research—one that is broader than an individual disorder or therapeutic area, resulting in higher placebo response across all areas of research over time.

How does an individual patient's level of expected improvement modify response to a placebo? Statements and actions from investigators, site staff, caregivers, and family members may significantly contribute to a patient's level of therapeutic expectation (defined as the level of improvement the patient anticipates in response to any treatment). Placebo response mitigation strategies must incorporate investigator training, site training, and patient/caregiver training in order to be effective. Some studies may be more prone to confounding due to therapeutic expectation than others. Pain studies are particularly susceptible to therapeutic expectation, with reported overall rates varying based on treatment modality.

Improving outcomes in clinical trials and reducing the trend toward high placebo response across different therapeutic areas requires the involvement of multiple stakeholders. As stated initially, the randomized, placebo-controlled clinical trial is the pivotal event in drug discovery; it often represents the culmination of lengthy preclinical investigation, immense investment of labor, intellectual capital, and considerable financial resources.

Source: https://www.wcgclinical.com/wp-content/uploads/2022/03/myths-and-realities-of-placebo-response-a-21st-century-prescription.pdf

Amgen Data on Bone Density for MariTide Moves Stock

Elaine Chen, "A scrap of data on Amgen's obesity drug candidate wipes out $12 billion in market value," *Stat+*, Nov 12, 2024 (excerpt)

On Tuesday, a tiny shred of data on Amgen's lead obesity candidate — not yet verified — erased $12 billion in market value.

The data, spotted by an analyst at Cantor Fitzgerald, focused on concerns about potential side effects with the drug, called MariTide. Once they were shared widely in an investor note, the company's shares fell 7%, a reminder that its stock is in a highly precarious position ahead of a critical readout of the therapy.

Analyst Olivia Brayer found the data, which were previously unreported, in hidden tabs of a file attached to a Nature Metabolism publication of early trial results for MariTide. The hidden tabs contained what appeared to be results showing study participants experiencing loss of bone mineral density, especially among those in the group taking the highest doses of the drug, Brayer said. The note arrived in inboxes at 2:11 p.m. ET, immediately triggering the selloff.

In a statement issued Wednesday morning, Amgen said it "does not see an association between the administration of MariTide and bone mineral density changes. The Phase 1 study results do not suggest any bone safety concern or change our conviction in the promise of MariTide."

Narimon Honarpour, Amgen's head of global development, said later Wednesday at an investor conference that the data tables referenced by the note were not finalized and were not subject to standard review, so the company has asked the journal to issue a correction and add in the finalized data. There were overlapping margins of error between treatment and placebo groups, leading researchers to conclude there was no association, he added.

Randy Seeley, director of the Michigan Nutrition Obesity Research Center, told STAT it's too early to read into the data because there are so few participants whose results were included and because there doesn't appear to be a clear dose effect. He also noted that patients undergoing any kind of major weight loss intervention, such as bariatric surgery, tend to lose bone density. Seeley has a research agreement with Amgen to study MariTide, but is not involved in any of the clinical trials.

Source: https://www.statnews.com/2024/11/12/amgen-maritide-obesity-drug-candidate-data/

When writing our July obesity market review, we too reviewed the appendicized data tables put out by Amgen in its *Nature Metabolism* paper (see p. 29 of our report).

To be clear, we didn't spot the hidden sheet but were puzzled to see a pharma company put out something that looked like raw output from a stat analysis package in a journal. We had never seen anything of the sort before.

Our analysis of the worksheet led us to comment that it's strange that insulin levels didn't drop with MariTide administration even though patients lost so much weight (the GIP antagonism MOA should involve insulin declines).

We noted the very small sample sizes and didn't take the findings that seriously. We noted that Amgen's upcoming Phase 2 data will be critical in analyzing the program.

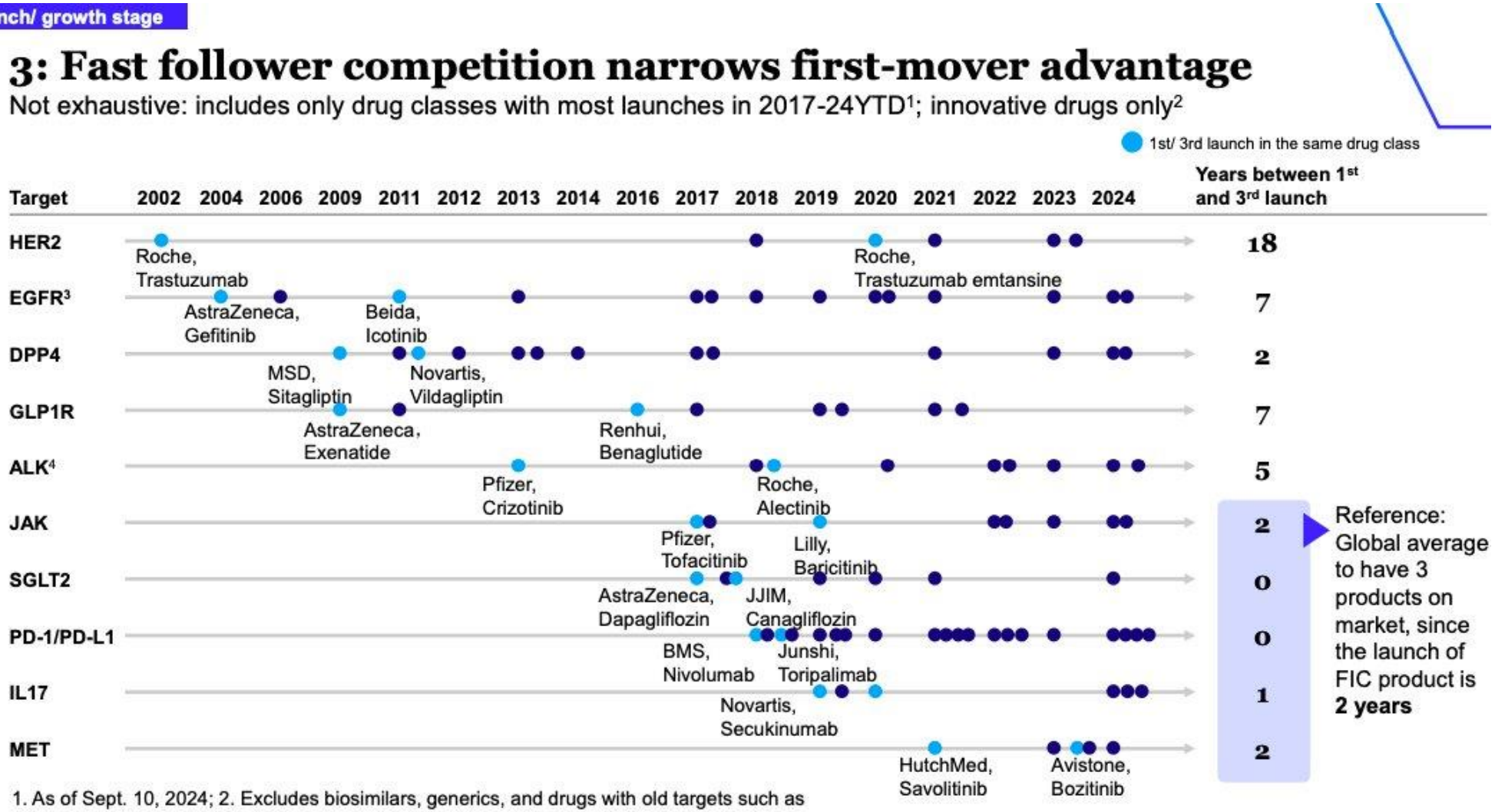
There is no obvious mechanistic reason to think that MariTide would impair bone density.

Substantial Narrowing of Period of Branded Exclusivity Due to Chinese Competition and Fast Follower Strategy

Launch/ growth stage

3: Fast follower competition narrows first-mover advantage

Not exhaustive: includes only drug classes with most launches in 2017-24YTD[1]; innovative drugs only[2]



1. As of Sept. 10, 2024; 2. Excludes biosimilars, generics, and drugs with old targets such as CHRM/ADRB/NR3C, NS3/4A, NS5A, NS5B, NRTIs 3. Excludes drugs targeting only EGFR exon20ins; 4. Includes drugs with targets of ROS1 and MET along with ALK

Sources: GBI; McKinsey analysis

US Confirms First Case of More Aggressive Mpox Strain

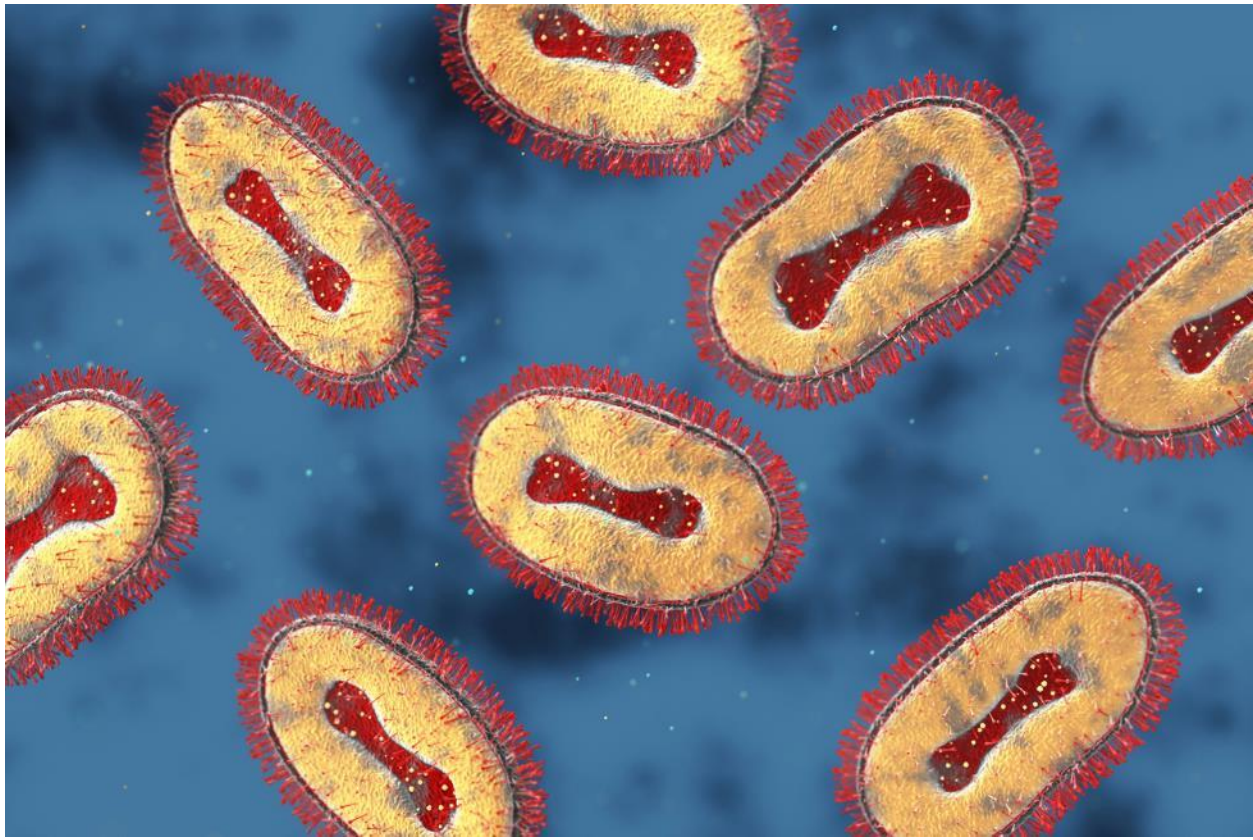
Filip Timotija, *The Hill*, Nov 16, 2024 (excerpt)

U.S. health officials confirmed on Saturday the first case of a more severe strain of mpox that infected an individual who recently traveled to Africa.

California health authorities identified the first known case of clade I mpox in the U.S. through laboratory testing. The person was treated in San Mateo County, according to the California Department of Public Health (CDPH). The individual is at home and recovering.

The case of clade I mpox outbreak started in Central and Eastern Africa.

“Historically, clade I has caused more severe illness than clade II, however, recent infections from clade I mpox may not be as clinically severe as in previous outbreaks, especially when cases have access to quality medical care,” CDPH wrote on Saturday.



Source: https://thehill.com/policy/healthcare/4994401-us-confirms-first-case-of-more-aggressive-mpox-strain/

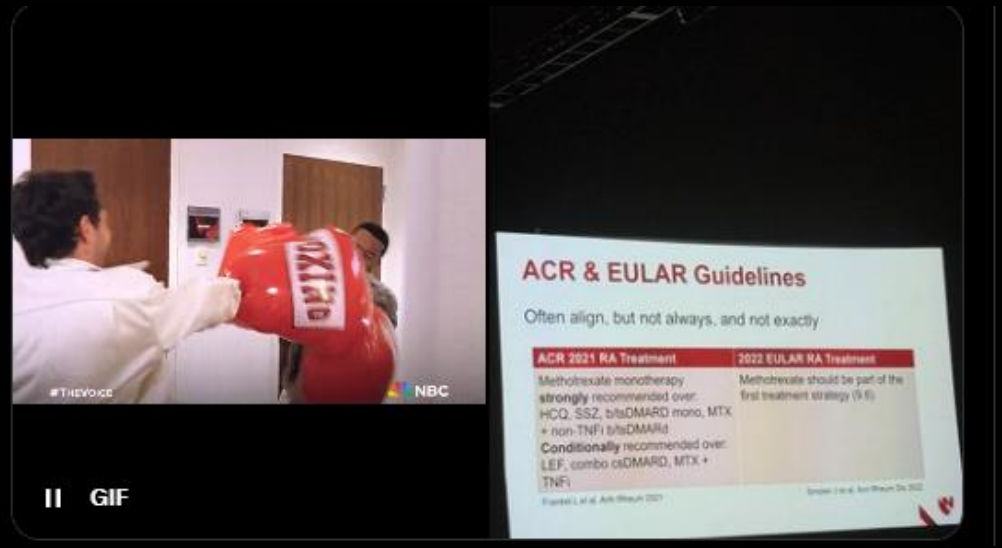
American College of Rheumatology Convergence Conference Underway

Those Rheumatologists Don’t Always Agree

Rheum Cat @rheum_cat · Nov 16

“Put two rheumatologists in a room and ask them about GC tapers and you’ll get an argument. Three and you’ll get a fight.” – Peter Merkel #ACR24 plenary

4 27 104 5.5K

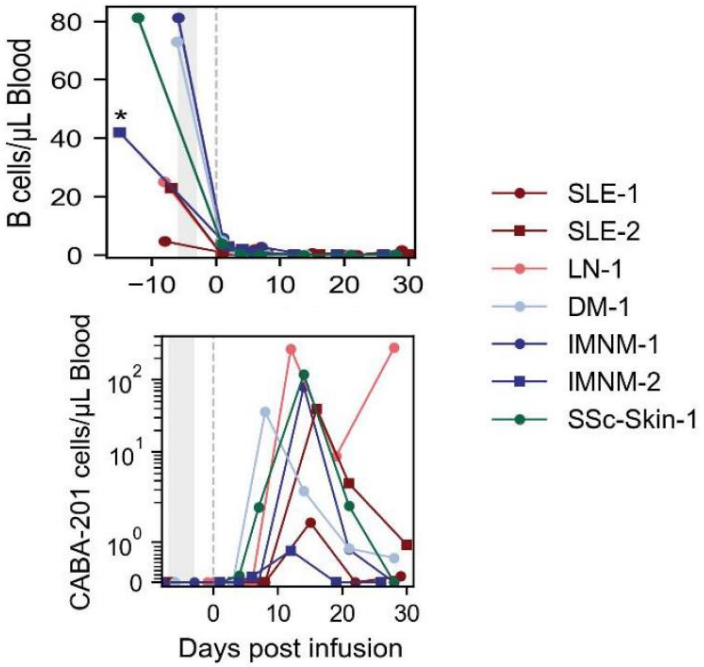


ACR: Cabeletta Data Wows Attendees

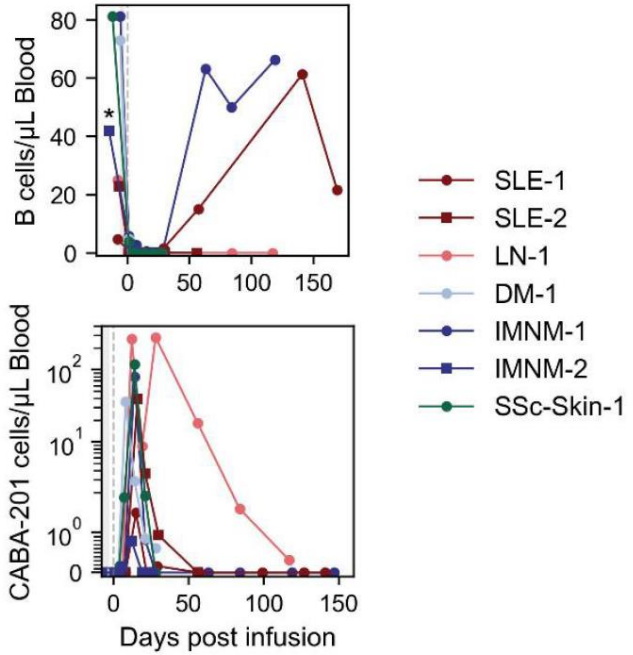
Consistent and Complete B cell Depletion by Day 22[1]

In patients with >3-month follow-up, B cell repopulation with naïve cells started as early as 8 weeks

B cell depletion & CABA-201 expansion through Day 30



B cell depletion/repopulation & CABA-201 expansion through Day 150



CABA-201 exhibited a PK/PD profile with peak expansion between Day 8 and 15 as expected, with a later 2nd peak for LN-1

PK, pharmacokinetic; PD, pharmacodynamic.
*Pre-infusion B-cell levels were measured at pre-preconditioning for all subjects other than IMNM-2 where apheresis was used.
1. Nunez et al. Correlative Studies of CABA-201 from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. Presented at ACR Convergence 2024. Abstract 0324.

This data matches the kind of B cell depletion seen in earlier studies with CAR-t for immunology seen by Georg Schett of Erlangen.

It's taken Cabaletta some time to generate the requisite data, but it has gotten there.

The results have not disappointed.

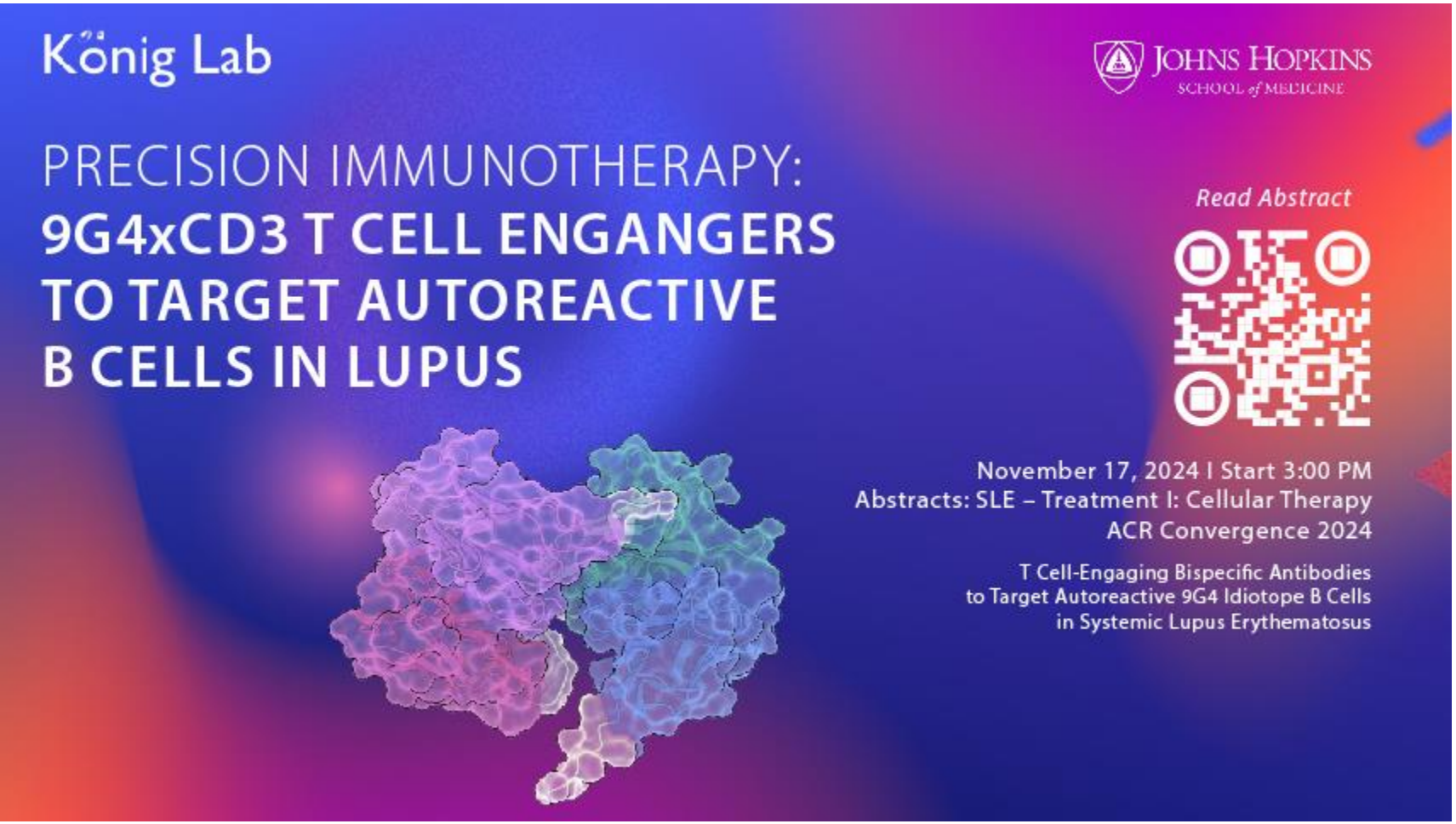
Summary from Clinical and Translational Data on the First 8 Patients

- CABA-201 appears to have a favorable risk-benefit profile
  - In patients with recent fever or infections, delaying CAR T infusion should be considered
- CABA-201 provided compelling efficacy in highly active and refractory autoimmune patients through the follow-up period
- Initial data support the potential for drug-free clinical responses
  - All patients discontinued all immunosuppressants
  - SLE patients with longer follow-up: steroid taper completed or ongoing (prednisone 8mg/day)
- The PK/PD data support the current dose of CABA-201[1]

CAR, chimeric antigen receptor; PK, pharmacokinetic; PD, pharmacodynamic; SLE, systemic lupus erythematosus

1. Nunez et al. Correlative Studies of CABA-201 from the RESET-Myositis™ and RESET-SLE™ Clinical Trials. Presented at ACR Convergence 2024. Abstract 0324

ACR: New Type of T-Cell Engager Used for Lupus.



immunotherapy approach for the selective depletion of autoreactive B cells in SLE. 9G4xCD3 BsAbs are efficient and specific at eliminating 9G4 B cells—an opportunity to treat SLE without increasing the risk of infection. Different to CAR-T cells, 9G4xCD3 BsAbs can be produced and administered at scale. Beyond autoimmune diseases, these BsAbs have utility in the treatment of B cell lymphomas.

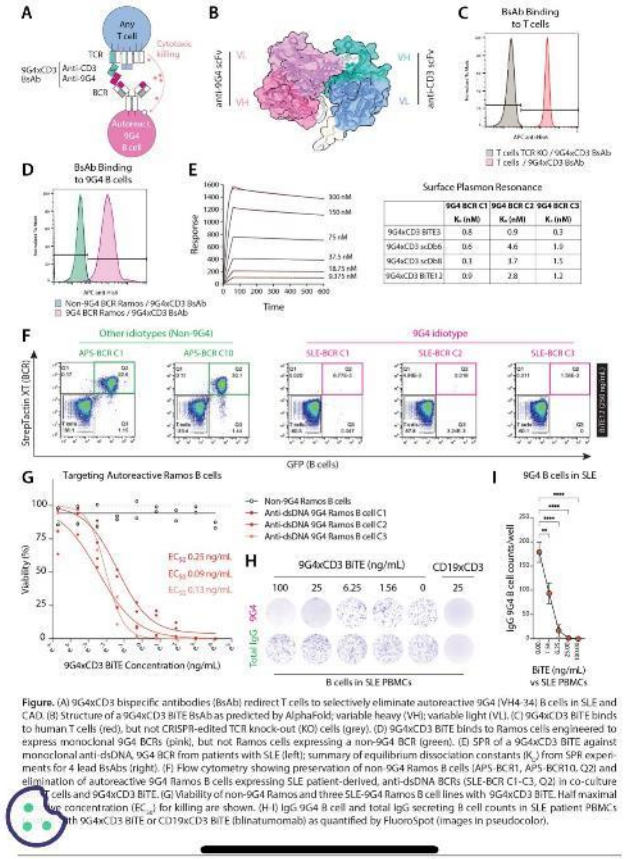


Figure. (A) 9G4xCD3 bispecific antibodies (BsAb) redirect T cells to selectively eliminate autoreactive 9G4 (VH4-34) B cells in SLE and CAD. (B) Structure of a 9G4xCD3 BiTE BsAb as predicted by AlphaFold; variable heavy (VH); variable light (VL). (C) 9G4xCD3 BiTE binds to human T cells (red), but not CRISPR-edited TCR knock-out (KO) cells (grey). (D) 9G4xCD3 BiTE binds to Ramos cells engineered to express monoclonal 9G4 BCRs (pink), but not Ramos cells expressing a non-9G4 BCR (green). (E) SPR of a 9G4xCD3 BiTE against monoclonal anti-dsDNA, 9G4 BCR from patients with SLE (left); summary of equilibrium dissociation constants (K_D) from SPR experiments for 4 lead BsAbs (right). (F) Flow cytometry showing preservation of non-9G4 Ramos B cells (APS BCR1, APS-BCR10, Q2) and elimination of autoreactive 9G4 Ramos B cells expressing SLE patient-derived, anti-dsDNA BCRs (SLE-BCR C1-C3, Q2) in co-culture with T cells and 9G4xCD3 BiTE. (G) Viability of non-9G4 Ramos and three SLE-9G4 Ramos B cell lines with 9G4xCD3 BiTE. Half maximal effector concentration (EC_{50}) for killing are shown. (H-I) IgG 9G4 B cell and total IgG secreting B cell counts in SLE patient PBMCs with 9G4xCD3 BiTE or CD19xCD3 BiTE (blinatumomab) as quantified by FluoroSpot (images in pseudocolor).

Levicept's Novel Neurotrophin-3 Inhibitor Shines at ACR Conference

Globenewswire, Nov 14, 2024

SANDWICH, United Kingdom, Nov. 14, 2024 (GLOBE NEWSWIRE) -- Levicept Ltd, a biotechnology company focused on the development of LEVI-04, a first-in-class treatment for osteoarthritis, is presenting the results from its positive Phase II trial of LEVI-04 at the American College of Rheumatology's annual meeting, ACR Convergence 2024, being held from 14 November to 19 November, 2024 in Washington,

DC. Headline results were first announced in August 2024.

LEVI-04 is a proprietary p75 neurotrophin receptor fusion protein (p75NTR-Fc) that provides analgesia via inhibition of NT-3 activity, supplementing the endogenous p75NTR binding protein and modulating excess neurotrophin levels present in osteoarthritis.

The data being presented at the conference are from Levicept's multiarm, multicentre, randomized, double-blind, placebo-controlled, Phase II study which enrolled 518 participants with pain and disability due to osteoarthritis of the knee (ClinicalTrials.gov ID: NCT05618782).

LEVI-04 demonstrated significant differences to placebo for the primary endpoint for all doses:

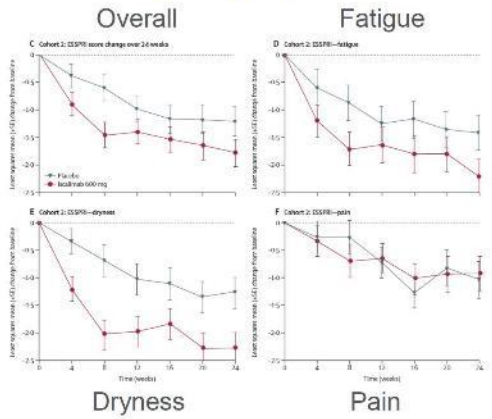
- The primary endpoint was WOMACi pain assessment (change from baseline at Week 17).
- The mean reduction in WOMAC pain score from baseline was greater than 50% for all three doses of LEVI-04 (0.3mg/kg, 1mg/kg, 2mg/kg) and all statistically different to placebo ($p<0.05$ vs placebo, all doses).
- More than 50% of the LEVI-04-treated patients reported ≥50% reduction in pain and >35% reported ≥70% reduction at week 17.
- Secondary endpoints included WOMAC subscales of function and joint stiffness, patient global assessment and daily pain scores and these were all statistically different to placebo.

Standard safety monitoring plus peripheral nervous system assessments showed LEVI-04 to be well tolerated. There was no increased incidence of SAEs, TEAEs and joint pathologies including rapidly progressive OA compared to placebo as measured via detailed, closely examined, radiographic analysis.

Source: https://www.manilatimes.net/2024/11/14/tmt-newswire/globenewswire/levicept-presents-positive-phase-ii-data-for-novel-neurotrophin-3-inhibitor-levi-04-for-treatment-of-patients-with-moderate-to-severe-osteoarthritis-at-acr-convergence-2024/2004798

ACR Presentation Highlights Progress in Sjogren's

Iscalimab for Sjögrens: Cohort 2: High Symptom Burden



Improvement in Fatigue and Dryness but not Pain

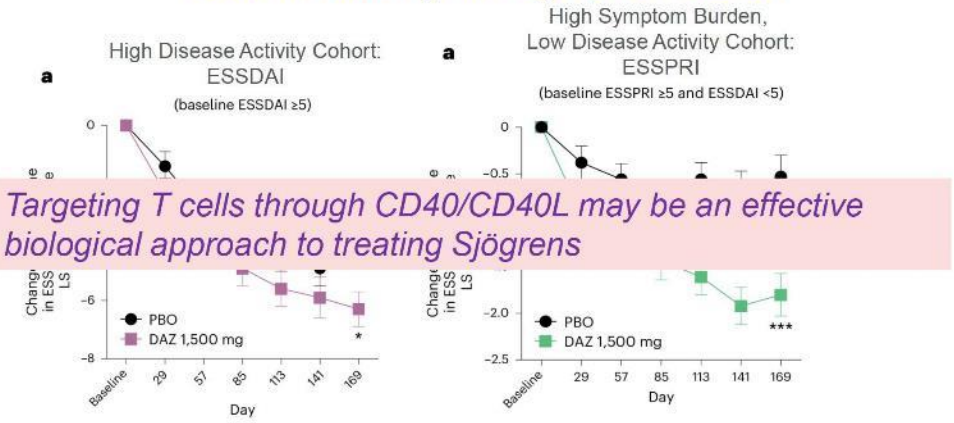
Placebo

Iscalimab

ESSPRI=EULAR Sjögrens Syndrome Patient Reported Index

Fisher et al, Lancet 2024;404:540-553

Dazodalibep (CD40L antagonist) Reduces Sjögrens Disease Activity and Symptom Burden



Targeting T cells through CD40/CD40L may be an effective biological approach to treating Sjögrens

St Clair et al, Nature Med 2024;30(6):1583-1592

MITIGATE Primary Outcome—Inebilizumab Reduces IgG4-RD Flare Rate

This first randomized, double-blind, placebo-controlled trial for IgG4-RD demonstrated efficacy of a CD19-targeted B cell depletion strategy.

All key secondary endpoints met, including less glucocorticoid use

Adverse events generally mild but included more UTIs and opportunistic infections in the INEB group

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inebilizumab for Treatment of IgG4-Related Disease

Authors: John H. Stone, M.D., M.P.H., Arezou Khosroshahi, M.D., Wen Zhang, M.D., Ph.D., Emanuel Della Torre, M.D., Ph.D., Kazuichi Okazaki, M.D., Ph.D., Yoshiya Tanaka, M.D., Ph.D., J. Matthias Löhr, M.D., Ph.D., +17, for the MITIGATE Trial Investigators

Published November 14, 2024 | DOI: 10.1056/NEJMoa2409712 | Copyright © 2024

J Stone et al-ACR Convergence 2024 Abstract # 0775

SJOGREN'S SYNDROME

Inebilizumab for Treatment of IgG4-Related Disease

John Stone et.al., *New England Journal of Medicine*, Nov 14, 2024 (excerpt)

IgG4-related disease is a multiorgan, relapsing, fibroinflammatory, immune-mediated disorder with no approved therapy. Inebilizumab targets and depletes CD19+ B cells and may be effective for treating patients with IgG4-related disease.

In this phase 3, multicenter, double-blind, randomized, placebo-controlled trial, adults with active IgG4-related disease underwent randomization in a 1:1 ratio to receive inebilizumab (300-mg intravenous infusions on days 1 and 15 and week 26) or placebo for a 52-week treatment period.

A total of 135 participants with IgG4-related disease underwent randomization: 68 participants were assigned to receive inebilizumab and 67 were assigned to receive placebo. Treatment with inebilizumab reduced flare risk; 7 participants (10%) in the inebilizumab group had at least one flare, as compared with 40 participants (60%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.06 to 0.28; P<0.001). The annualized flare rate was lower with inebilizumab than with placebo (rate ratio, 0.14; 95% CI, 0.06 to 0.31; P<0.001).

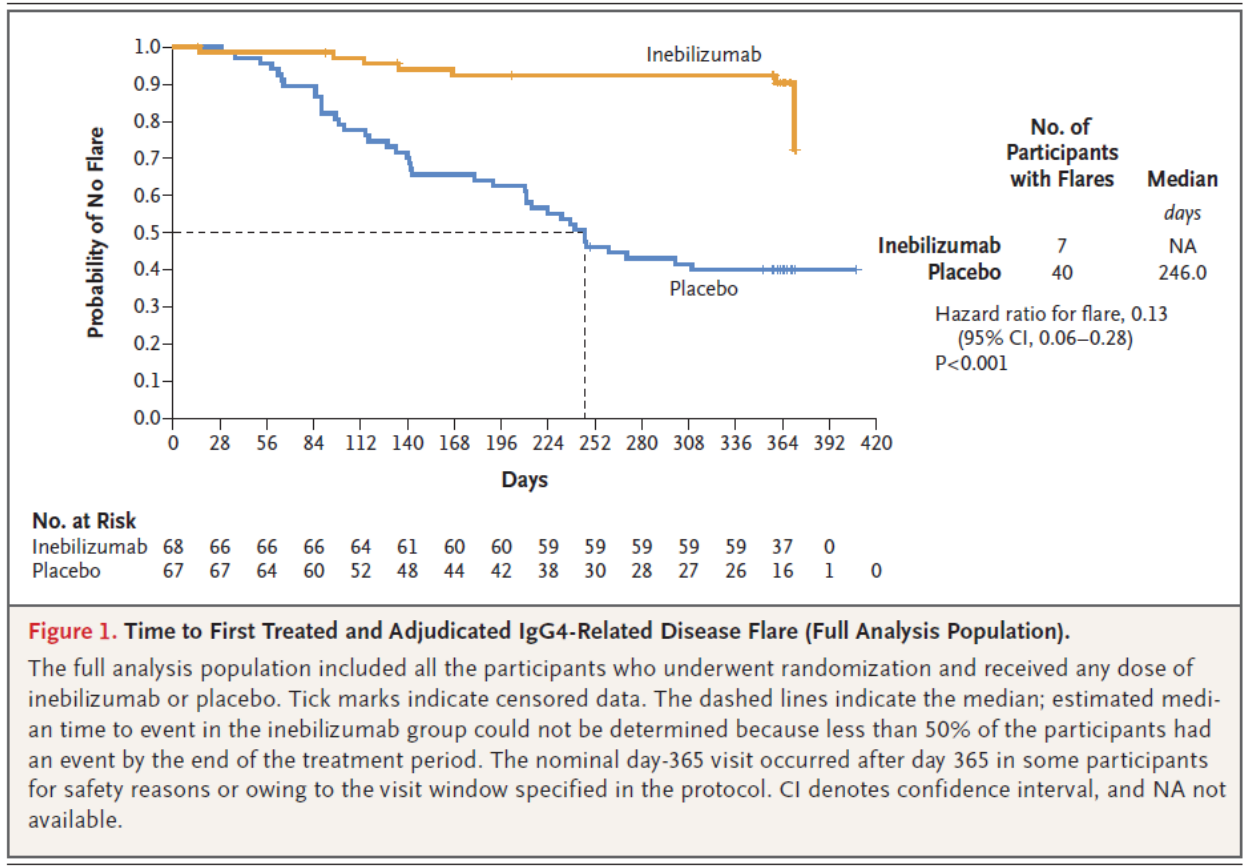


Figure 1. Time to First Treated and Adjudicated IgG4-Related Disease Flare (Full Analysis Population).

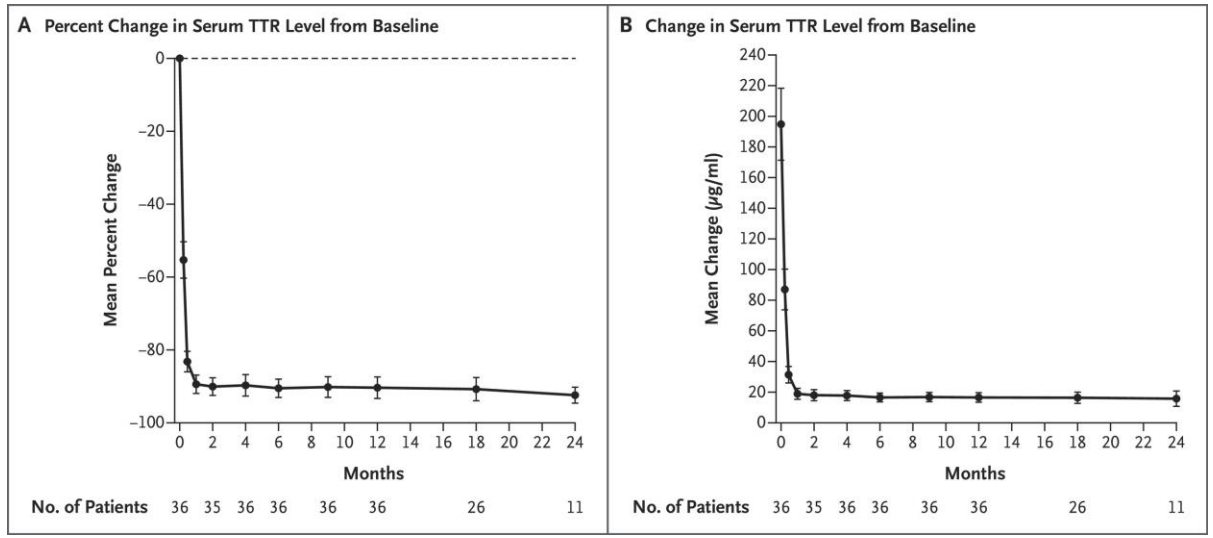
The full analysis population included all the participants who underwent randomization and received any dose of inebilizumab or placebo. Tick marks indicate censored data. The dashed lines indicate the median; estimated median time to event in the inebilizumab group could not be determined because less than 50% of the participants had an event by the end of the treatment period. The nominal day-365 visit occurred after day 365 in some participants for safety reasons or owing to the visit window specified in the protocol. CI denotes confidence interval, and NA not available.

Source: https://pubmed.ncbi.nlm.nih.gov/39541094/

AHA: CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

M. Fontana et.al., *NEJM*, Nov 16, 2024 (excerpt)

A total of 36 patients received nex-z and completed at least 12 months of follow-up. Of these patients, 50% were in NYHA class III and 31% had variant ATTR-CM. The mean percent change from baseline in the serum TTR level was −89% (95% confidence interval [CI], −92 to −87) at 28 days and −90% (95% CI, −93 to −87) at 12 months. Adverse events were reported in 34 patients. Five had transient infusion-related reactions, and two had transient liver-enzyme elevations that were assessed as treatment-related. Serious adverse events, most of which were consistent with ATTR-CM, were reported in 14 patients. The geometric mean factor change from baseline to month 12 was 1.02 (95% CI, 0.88 to 1.17) in the NT-proBNP level and 0.95 (95% CI, 0.89 to 1.01) in the high-sensitivity cardiac troponin T level. The median change from baseline to month 12 in the 6-minute walk distance was 5 m (interquartile range, −33 to 49). A total of 92% of the patients had either improvement or no change in their NYHA class.



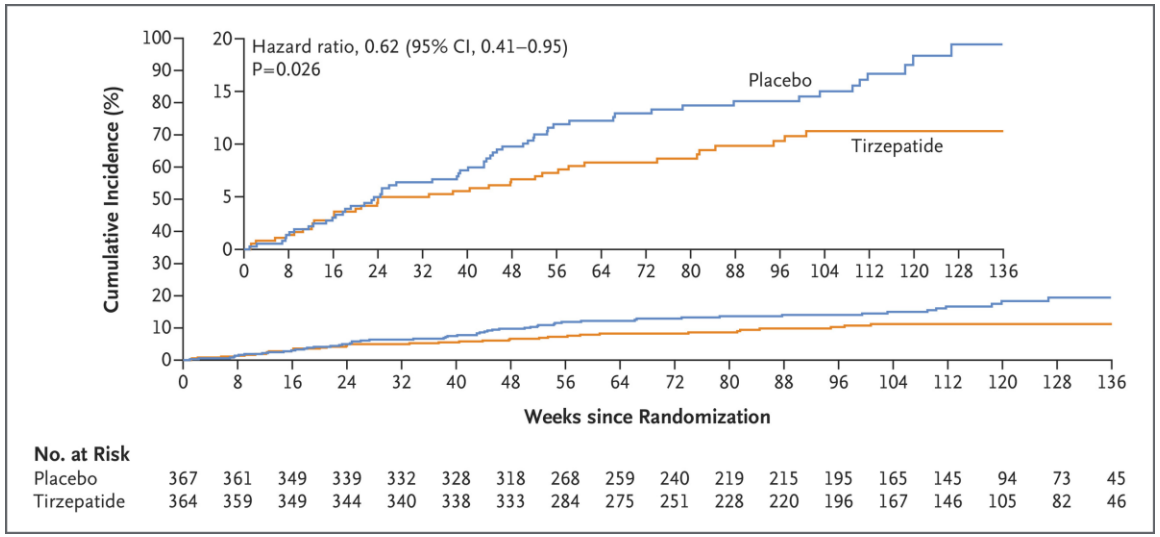
Very strong data for Intellia Drug Candidate

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2412309

AHA: Tirzepatide Makes a Huge Dent in Heart Disease

M. Packer et.al., *NEJM*, Nov 16, 2024 (excerpt)

A total of 364 patients were assigned to the tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P=0.026). Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively (hazard ratio, 1.58; 95% CI, 0.52 to 4.83). At 52 weeks, the mean (±SD) change in the KCCQ-CSS was 19.5±1.2 in the tirzepatide group as compared with 12.7±1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.

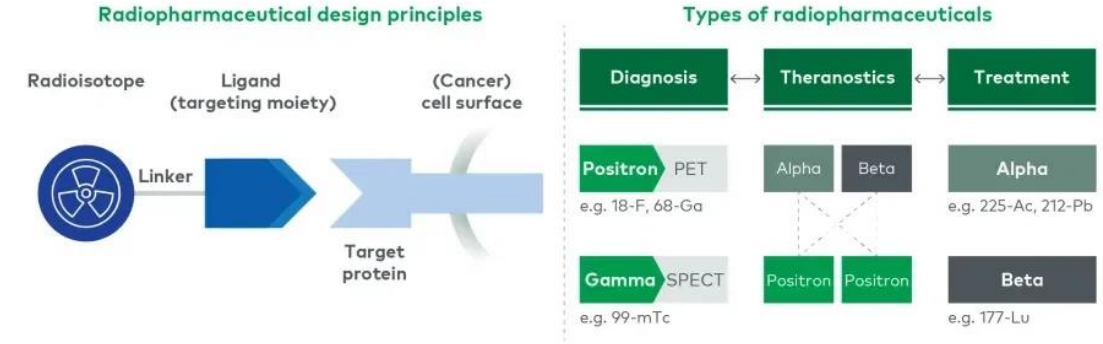


Very strong data for TZP in preventing heart disease

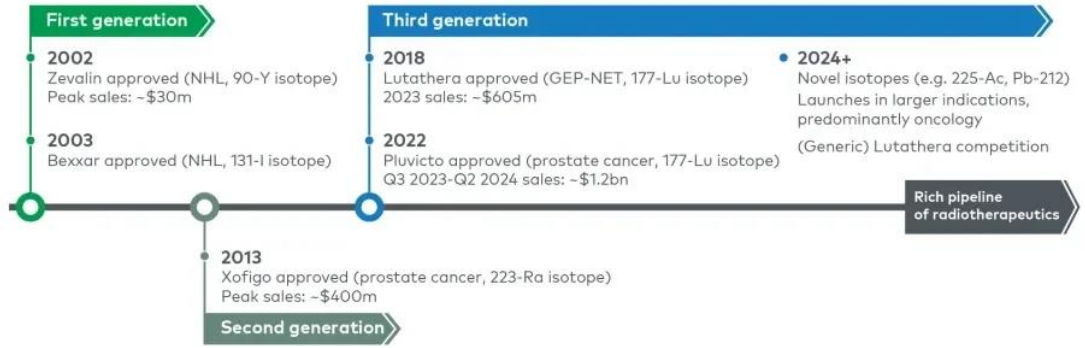
Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2410027

Last Week's LEK Report on RadioPharma

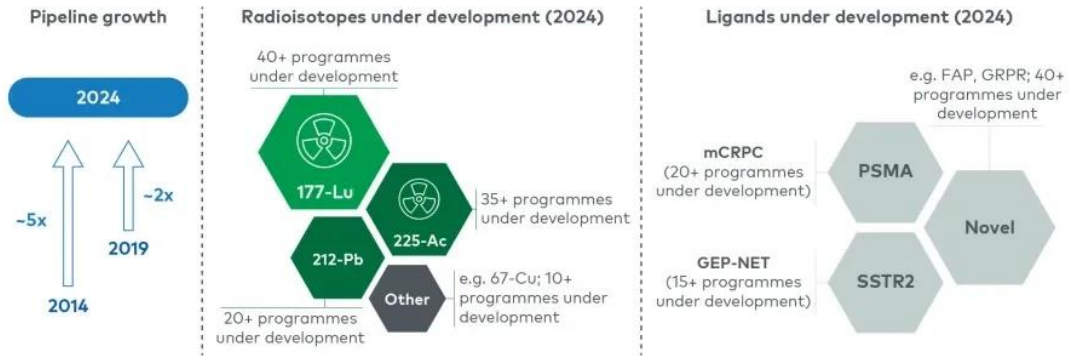
Anne Dhulesia and Thomas Van Tergouw, "From Niche to Widespread Use: The Turning Point for Radiotherapeutics," *LEK Report*, Nov 12, 2024 (excerpt)



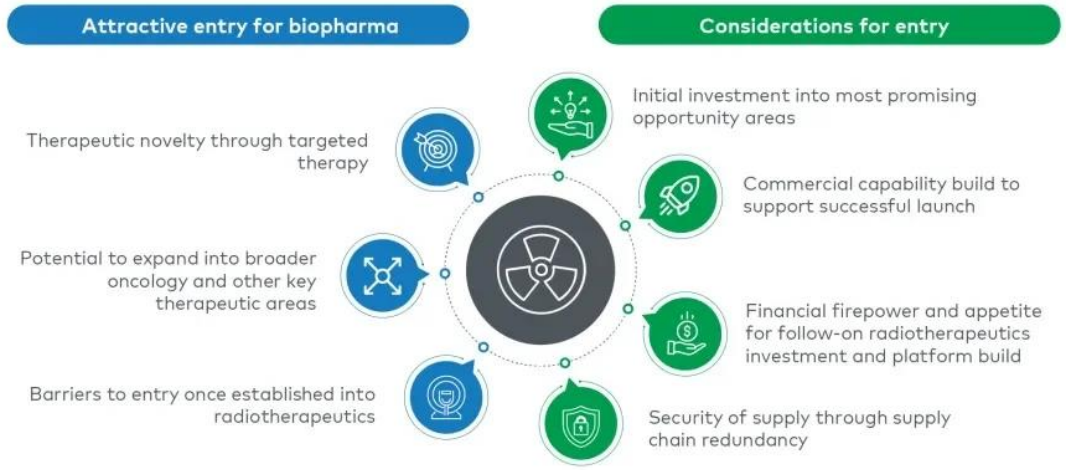
Note: PET=positron emission tomography, SPECT=single photon emission computed tomography
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports



Note: NHL=non-Hodgkin lymphoma, GEP-NET=gastroenteropancreatic neuroendocrine tumour
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports



Note: mCRPC=metastatic castration-resistant prostate cancer, GEP-NET=gastroenteropancreatic neuroendocrine tumour, FAP=fibroblast activation protein, GRPR=gastrin-releasing peptide receptor, PSMA=prostate specific membrane antigen, SSTR2=somatostatin receptor 2
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports



Source: L.E.K. research and analysis

Source: https://www.lek.com/insights/hea/global/ei/niche-widespread-use-turning-point-radiotherapeutics

Exercise Pays Off

Veerman L, Tarp J, Wijaya R, Wanjau MN, Möller H, Haigh F, Lucas P, Milat A. Physical activity and life expectancy: a life-table analysis. *Br J Sports Med*, Nov 14, 2024.

We applied a predictive model based on device-measured PA risk estimates and a life-table model analysis, using a life-table of the 2019 US population based on 2017 mortality data from the National Centre for Health Statistics. The participants included were 40+ years with PA levels based on data from the 2003–2006 National Health and Nutritional Examination Survey. The main outcome was life expectancy based on PA levels. If all individuals were as active as the top 25% of the population, Americans over the age of 40 could live an extra 5.3 years (95% uncertainty interval 3.7 to 6.8 years) on average. The greatest gain in lifetime per hour of walking was seen for individuals in the lowest activity quartile where an additional hour's walk could add 376.3 min (~6.3 hours) of life expectancy (95% uncertainty interval 321.5 to 428.5 min).

Table 2. Benefits achieved by lower active individuals when they move to higher physical activity (PA) levels

Change in PA (quartile)	Average extra 3 mph walking equivalence (min/day)	Prolonged life (min) per hour of walking	Life expectancy difference at age 40 (years)
1→ 2	28.5 (27.4 to 29.7)	376.3 (321.5 to 428.5)	6.3 (5.1 to 7.5)
2→ 3	27.8 (26.8 to 28.7)	160.1 (10.4 to 278.4)	2.8 (0.1 to 5.5)
2→ 4	82.8 (78.2 to 87.3)	96.1 (59.9 to 136.0)	4.6 (2.7– to 6.8)
3→ 4	55.0 (50.4 to 59.5)	57.1 (−37.0 to 136.9)	1.9 (−1.0 to 4.6)
1→ 4	111.2 (106.7 to 115.9)	169.1 (146.4 to 193.4)	10.9 (9.3 to 12.7)

- Health benefits achieved by lower active individuals of the American population age ≥40 years when they move to higher physical activity levels, taking the difference between quartile means. Values are reported as mean and 95% uncertainty intervals. The calculation of the minutes of walking equivalent, prolonged life (min) per hour of walking and the life expectancy difference in years is detailed in the Methods section.

To an even jaded observer, these data are amazing.

We all know that exercise matters but to see it be related to five to ten years of extra life is remarkable.

Source: https://bjsm.bmj.com/content/early/2024/10/07/bjsports-2024-108125.long

Eli Lilly and Novo Want to Shake off Ozempic Copycats. Are They Ready to Meet Demand?

David Wainer, *Wall Street Journal*, Nov 17, 2024 (excerpt)

Pharmaceutical companies are typically rewarded for their innovation with years of market exclusivity before cheaper generics enter the scene. But for diabetes and obesity drugs like Ozempic and Zepbound, known as GLP-1s, cheaper copycats emerged almost immediately.

This is due to a provision that permits drug compounders to produce copies during periods of shortage. For GLP-1s, supply constraints have persisted ever since Wegovy's approval for obesity in 2021, giving rise to a booming market for compounders.

That window for mass drug compounding, however, could start to close if the FDA upholds its recent determination that tirzepatide, the active ingredient in Eli Lilly's Zepbound and Mounjaro, is no longer in short supply. Although the FDA declared the shortage resolved a month ago, it is currently reassessing its decision after facing a lawsuit from a compounding trade group. An update is expected on Thursday. It is possible the FDA could reverse its decision or give compounders more time. The nomination of Robert F. Kennedy Jr.to serve as secretary of Health and Human Services, which has jurisdiction of the FDA, adds some uncertainty to what might happen under the Trump administration, given Kennedy's skepticism of big pharma and GLP-1s in particular.

Nonetheless, the days of mass compounding appear to be waning. Notably, the FDA also has recently listed Novo Nordisk's semaglutide—the active ingredient in Ozempic and Wegovy—as available on its website, though it hasn't formally declared the shortage to be over.

If the FDA moves to restrict mass compounding, it could spell trouble for telehealth companies like Hims & Hers Health and Ro, while providing a boost in demand for Lilly and Novo.

Although Lilly Chief Executive David Ricks played down the impact of compounding on its sales on a recent earnings call, the potential upside could be significant. Conservative estimates indicate that hundreds of thousands of patients are currently turning to compounders for access to these medications. Many patients prefer to go this route because insurance coverage of GLP-1 drugs for obesity isn't yet widespread and the compounded drugs are cheaper.

The bigger question is whether the manufacturers are equipped to meet heightened demand without falling back into shortages within a few months. Eli Lilly is planning to further fuel demand with new consumer-focused advertising in the coming weeks. UBS analyst Jo Walton captured the concern during Novo's earnings call last month, noting that demand next year could surge as Novo and Lilly ramp up advertising while compounders potentially exit. "Should we be concerned that it'll be only another three months before you're back into telling us that you're in short supply?" Walton said.

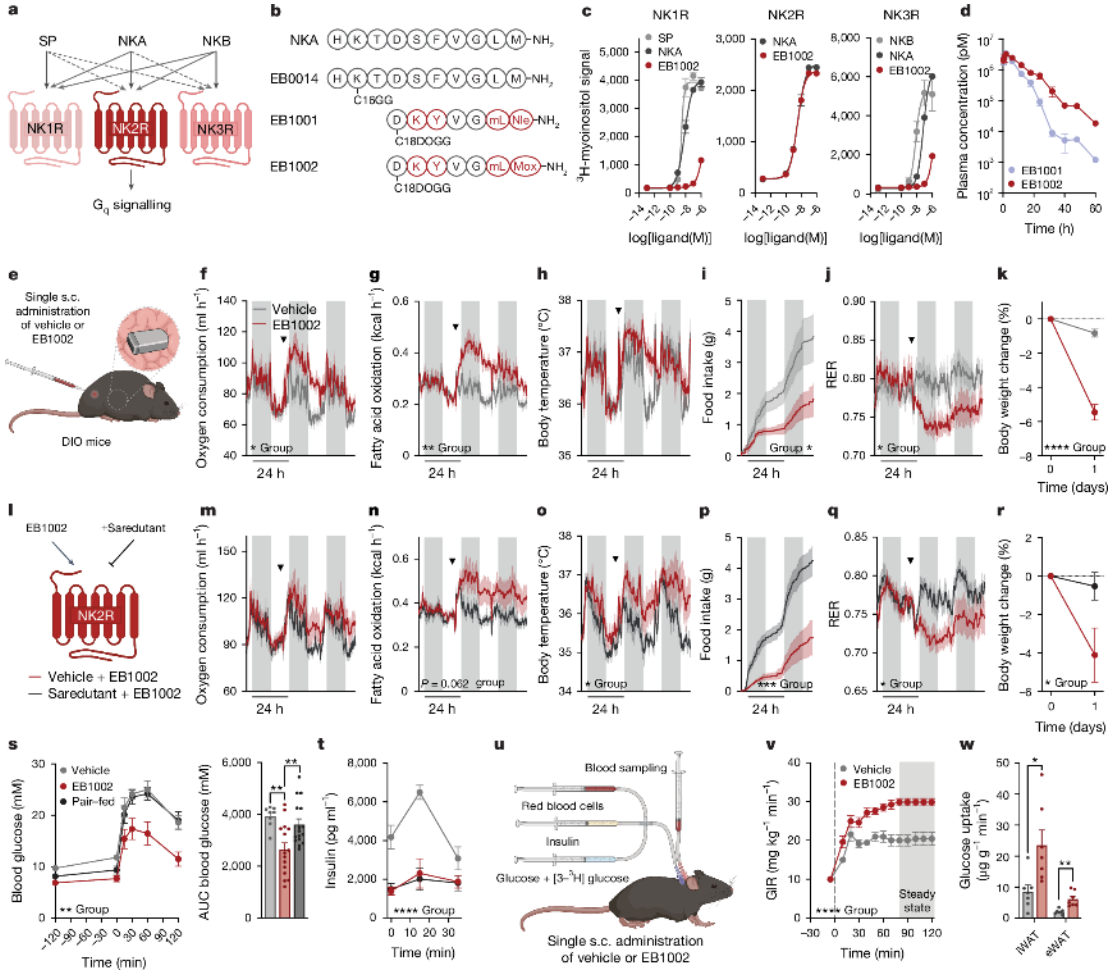
Source: https://www.wsj.com/health/pharma/eli-illy-novo-ozempic-zepbound-copycats-e6171fdd

Obesity Drugs: NK2R Control of Energy Expenditure and Feeding to Treat Metabolic Diseases

F. Sass et.al., *Nature*, Nov 13, 2024 (excerpt)

The combination of decreasing food intake and increasing energy expenditure represents a powerful strategy for counteracting cardiometabolic diseases such as obesity and type 2 diabetes1. Yet current pharmacological approaches require conjugation of multiple receptor agonists to achieve both effects2,3,4, and so far, no safe energy-expending option has reached the clinic. Here we show that activation of neurokinin 2 receptor (NK2R) is sufficient to suppress appetite centrally and increase energy expenditure peripherally. We focused on NK2R after revealing its genetic links to obesity and glucose control. However, therapeutically exploiting NK2R signalling has previously been unattainable because its endogenous ligand, neurokinin A, is short-lived and lacks receptor specificity5,6. Therefore, we developed selective, long-acting NK2R agonists with potential for once-weekly administration in humans. In mice, these agonists elicit weight loss by inducing energy expenditure and non-aversive appetite suppression that circumvents canonical leptin signalling. Additionally, a hyperinsulinaemic–euglycaemic clamp reveals that NK2R agonism acutely enhances insulin sensitization. In diabetic, obese macaques, NK2R activation significantly decrea body weight, blood glucose, triglycerides and cholesterol, and ameliorates insu resistance. These findings identify a single receptor target that leverages both energy-expending and appetite-suppressing programmes to improve energy homeostasis and reverse cardiometabolic dysfunction across species.

Fig. 2: Development and characterization of first-in-class selective, long-acting NK2R agonists.



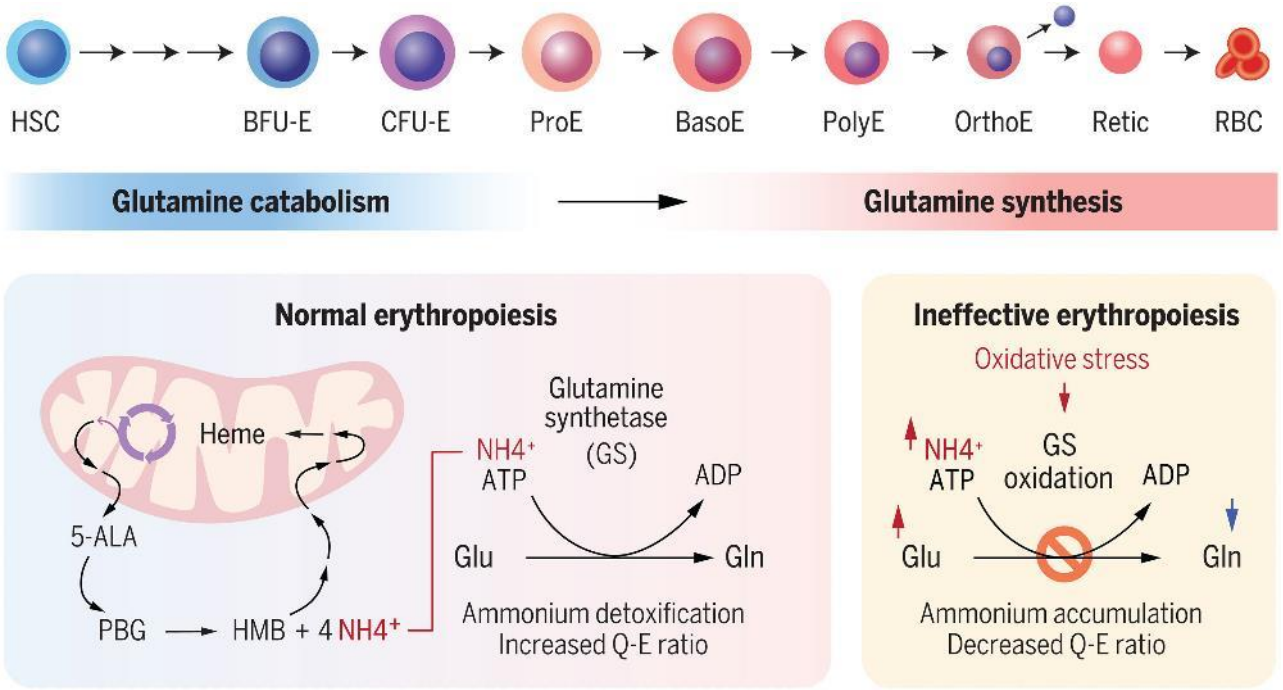
Source: https://www.nature.com/articles/s41586-024-08207-0

A Glutamine Metabolic Switch Supports Erythropoiesis

Junhua Lyu et.al, *Science*, Nov 15, 2024

A healthy human body is thought to make millions of red blood cells per second. To better understand how erythropoietic cells accomplish this feat, Lyu et al. characterized the transcriptional and metabolic profiles of erythroid precursor cells from mouse bone marrow. The cells showed enhanced production of the enzyme glutamine synthetase. Biochemical synthesis of heme to make hemoglobin causes the accumulation of ammonium, which causes oxidative stress. The authors propose that enhanced glutamine synthetase activity helps to consume the excess ammonium and prevents cell damage. Loss of glutamine synthetase in mice caused metabolic changes similar to those in erythrocytes from mice with beta-thalassemia, a blood disorder that causes anemia. Defective erythropoiesis in beta-thalassemia was ameliorated by antioxidants or expression of glutamine synthetase.

Source: https://www.science.org/doi/10.1126/science.adh9215

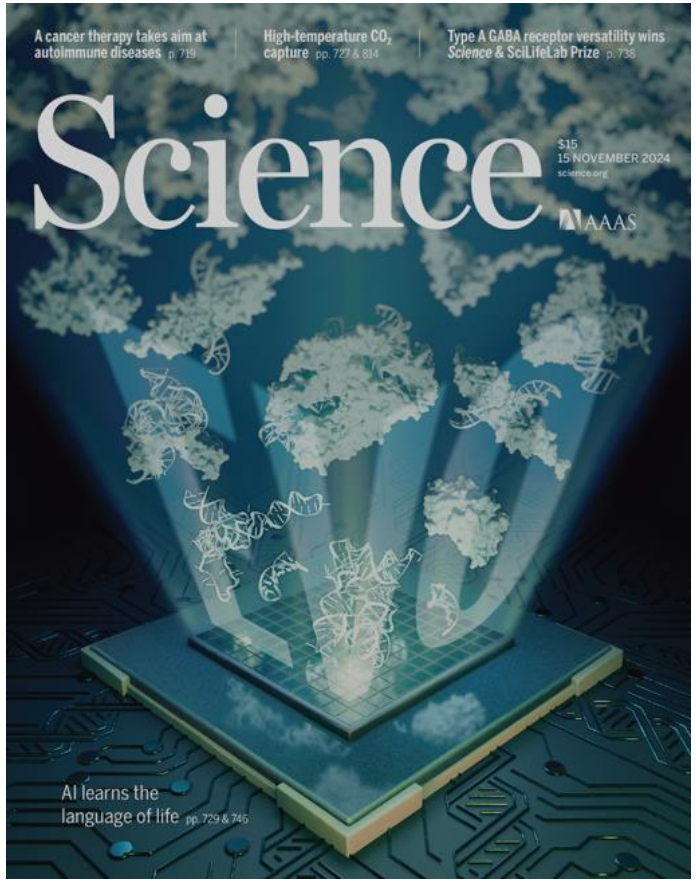


A glutamine metabolic switch is essential for erythropoiesis.
Differentiating erythroid cells up-regulate glutamine synthetase and down-regulate glutamine catabolism, resulting in increased glutamine-to-glutamate ratios during erythropoiesis. This metabolic switch is essential for detoxifying ammonium generated from heme biosynthesis through GS-catalyzed glutamate-ammonium ligation. In the major hemoglobinopathy β-thalassemia, GS is impaired by protein oxidation, causing glutamate and ammonium accumulation and decreased Q-E ratios in erythrocytes. 5-ALA, 5-aminolevulinic acid; NH_4^+, ammonium; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

Sequence Modeling and Design from Molecular to Genome Scale with Evo

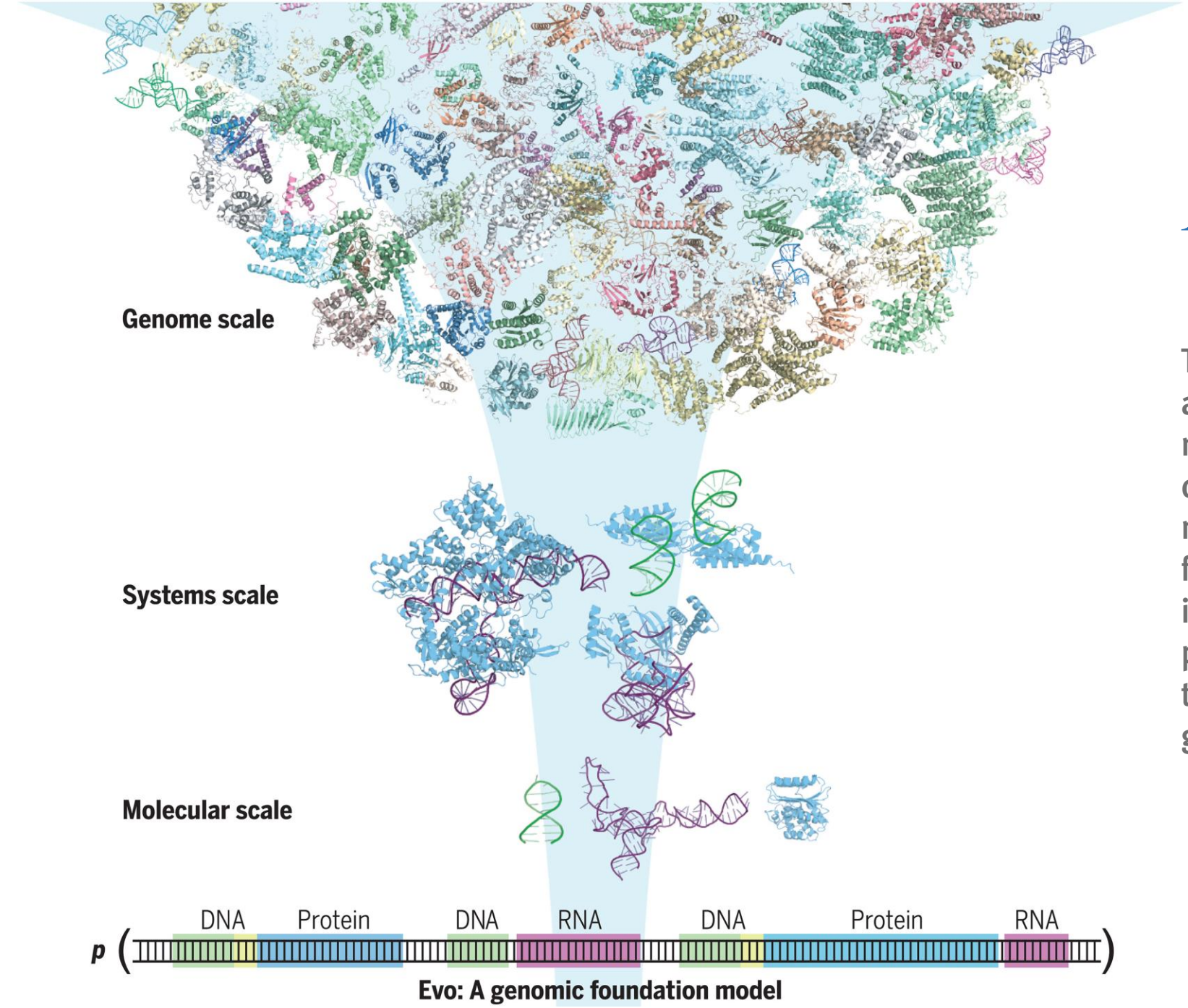
Eric Nguyen et.al, *Science*, Nov 15, 2024

Large language models have great potential to interpret biological sequence data. Nguyen et al. present Evo, a multimodal artificial intelligence model that can interpret and generate genomic sequences at a vast scale. The Evo architecture leverages deep learning techniques, enabling it to process long sequences efficiently. By analyzing millions of microbial genomes, Evo has developed a comprehensive understanding of life's complex genetic code, from individual DNA bases to entire genomes. This enables the model to predict how small DNA changes affect an organism's fitness, generate realistic genome-length sequences, and design new biological systems, including laboratory validation of synthetic CRISPR systems and IS200/IS605 transposons. Evo represents a major advancement in our capacity to comprehend and engineer biology across multiple modalities and multiple scales of complexity.



Evo is a genomic foundation model that enables prediction and generation tasks from the molecular to genome scale. Using an architecture based on advances in deep signal processing, Evo is trained on 7 billion parameters with a context length of 131 kilobases at single-nucleotide resolution. Evo captures two fundamental aspects of biology—the multimodality of the central dogma and the multiscale nature of evolution.

Source: https://www.science.org/doi/10.1126/science.ado9336



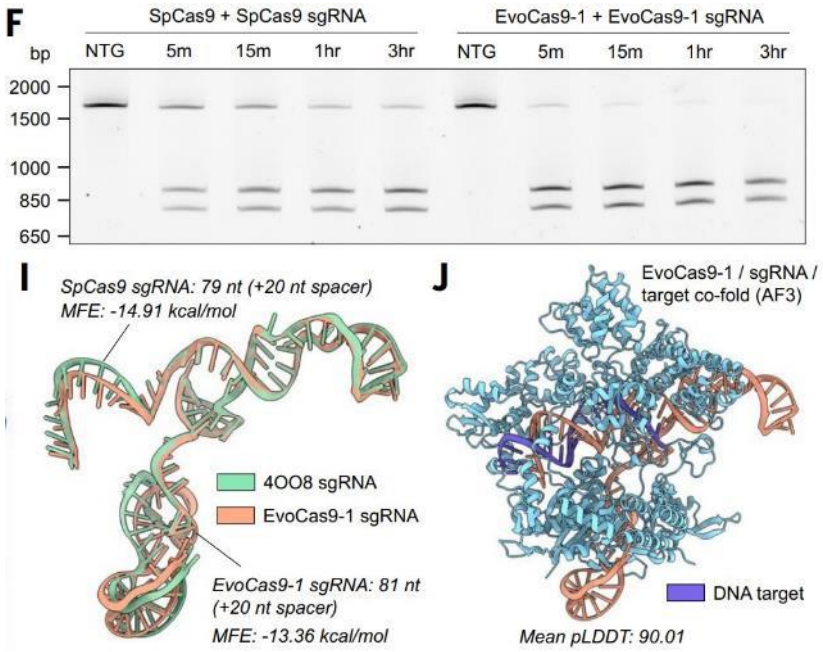
Meet Evo

Trained on 2.7 million raw prokaryotic and phage genome sequences, Evo is naturally multimodal, enabling the codesign of DNA, RNA, and protein molecules that form higher-order functional systems. Evo is also inherently multiscale, enabling prediction and generation tasks at the level of molecules, systems, and genomes.

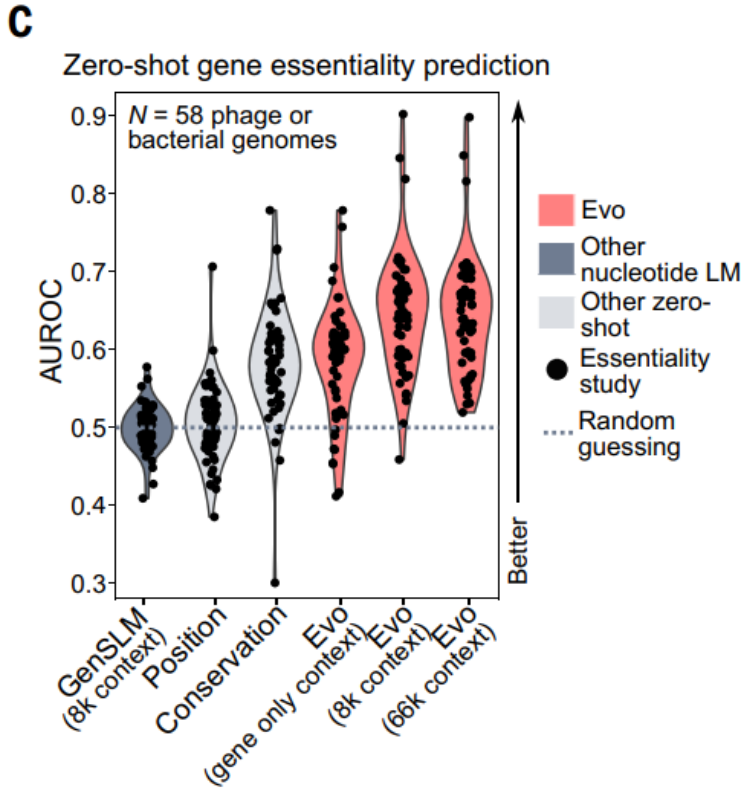
Source: https://www.science.org/doi/10.1126/science.ado9336

Evo Can…

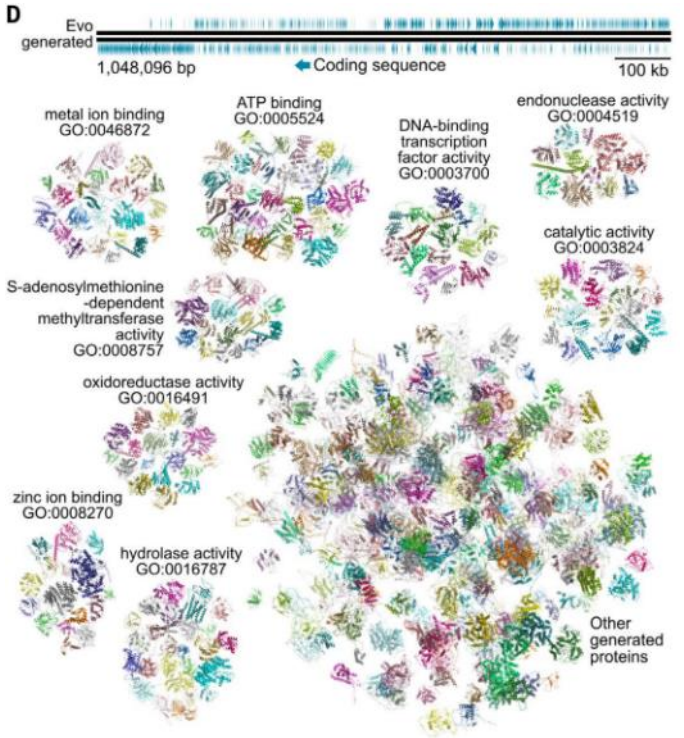
Design a functioning CRISPR-Cas enzyme from Scratch



Tell Which Genes Actually Matter for Physiology



Generate genome-length DNA sequences, encoding a diverse set of proteins



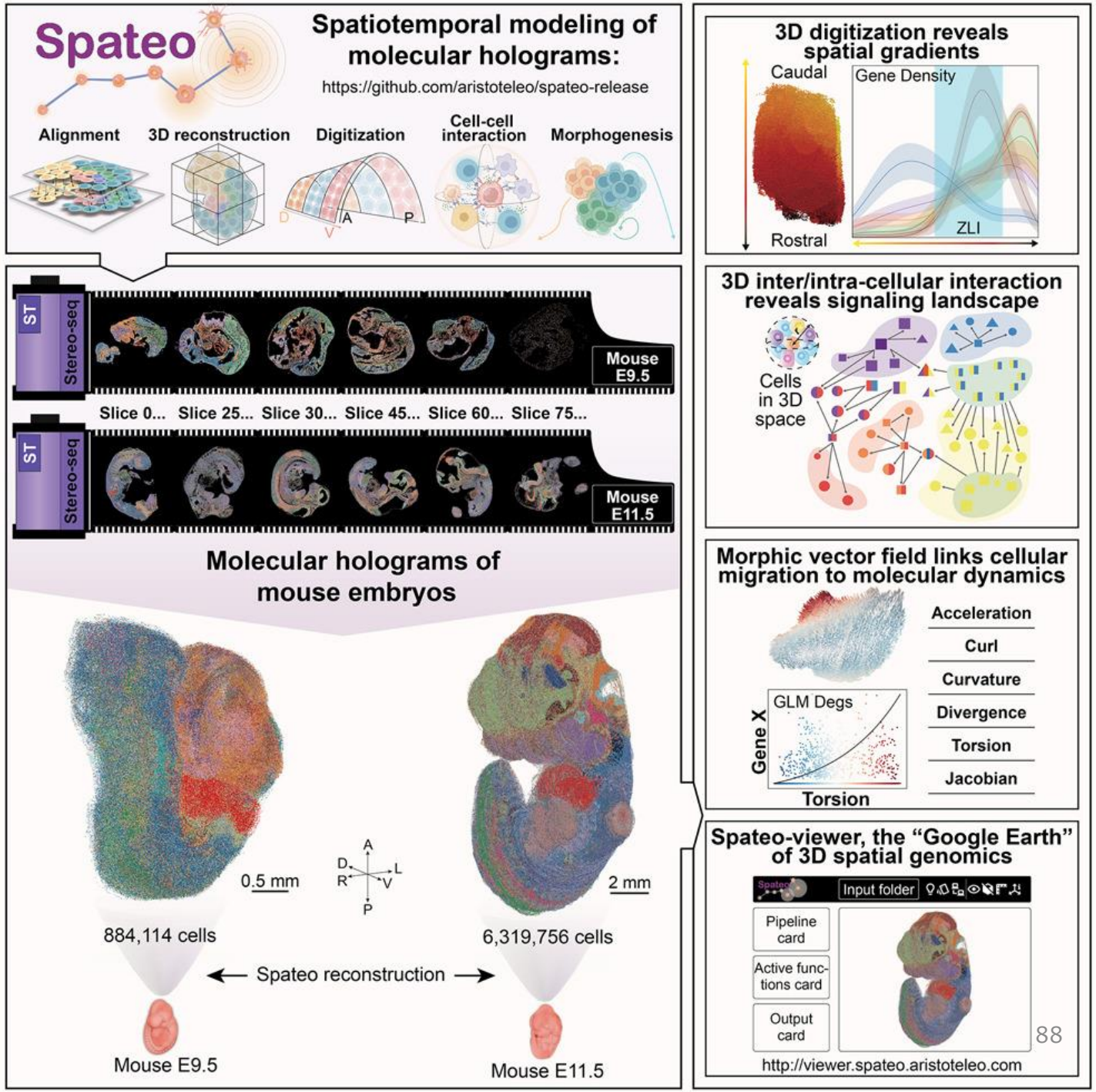
Source: https://www.science.org/doi/10.1126/science.ado9336

Spatiotemporal Modeling of Molecular Holograms

Qiu, X. et.al, *Cell*, Nov 11, 2024

Quantifying spatiotemporal dynamics during embryogenesis is crucial for understanding congenital diseases. We developed Spateo (https://github.com/aristoteo/spateo-release), a 3D spatiotemporal modeling framework, and applied it to a 3D mouse embryogenesis atlas at E9.5 and E11.5, capturing eight million cells. Spateo enables scalable, partial, non-rigid alignment, multi-slice refinement, and mesh correction to create molecular holograms of whole embryos. It introduces digitization methods to uncover multi-level biology from subcellular to whole organ, identifying expression gradients along orthogonal axes of emergent 3D structures, e.g., secondary organizers such as midbrain-hindbrain boundary (MHB). Spateo further jointly models intercellular and intracellular interaction to dissect signaling landscapes in 3D structures, including the zona limitans intrathalamica (ZLI). Lastly, Spateo introduces "morphometric vector fields" of cell migration and integrates spatial differential geometry to unveil molecular programs underlying asymmetrical murine heart organogenesis and others, bridging macroscopic changes with molecular dynamics. Thus, Spateo enables the study of organ ecology at a molecular level in 3D space over time.

Source: https://www.cell.com/cell/fulltext/S0092-8674(24)01159-0



Disclosure

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