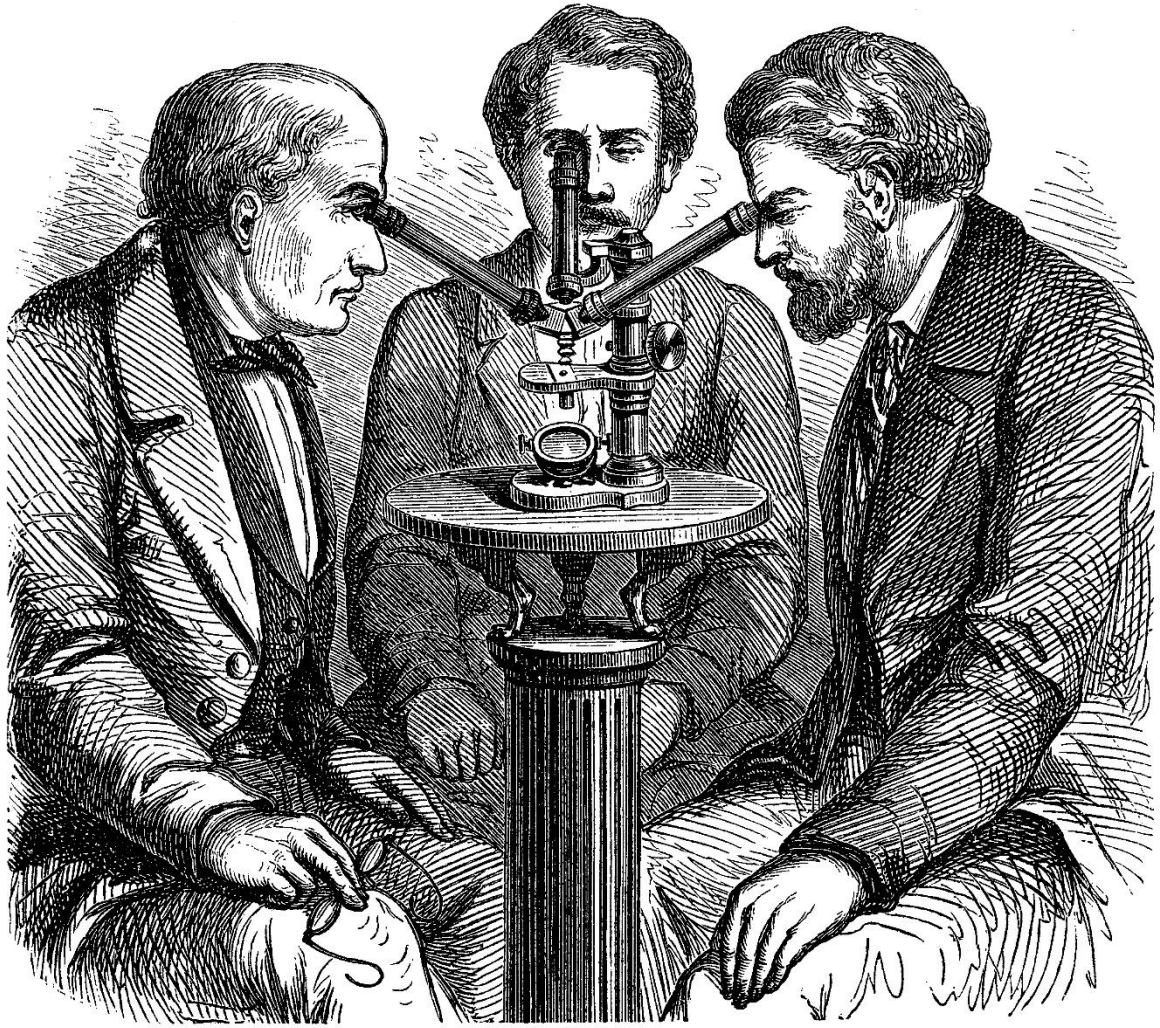
Biopharmaceutical Sector

Weekly Update – November 13, 2023

STIFEL | Healthcare

Table of Contents



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STIFEL | Healthcare

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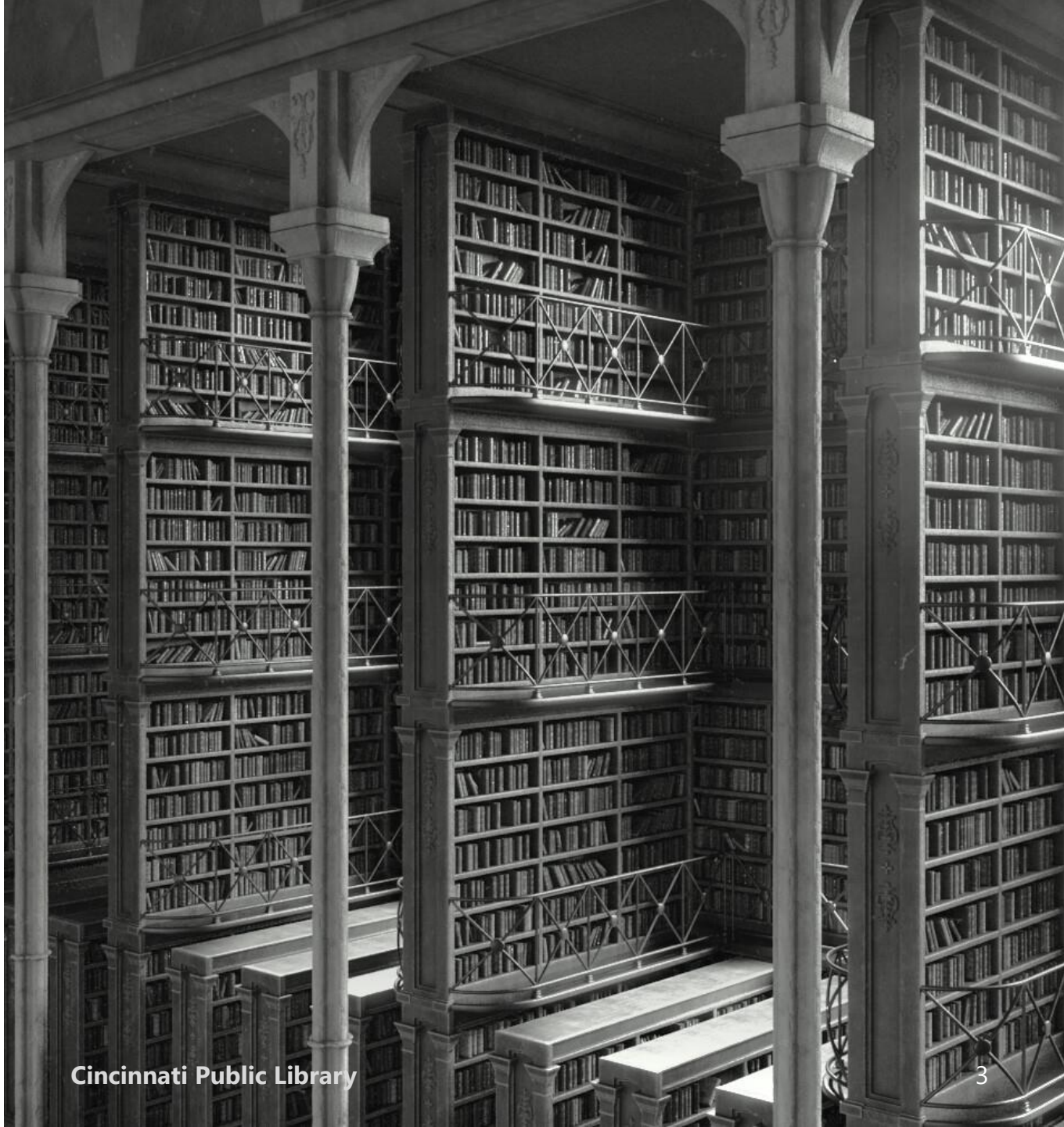
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
October 16, 2023 (Cancer Screening)
October 9, 2023 (Biosimilars, M&A)
October 2, 2023 (FcRn, Antibiotics)
September 25, 2023 (Target ID)
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)


Cincinnati Public Library

Join Us at These Upcoming Events

Biotech Hangout held its latest event on November 3rd.

The next event will be on November 10, 2023.

Some links:

November 3rd Replay: https://twitter.com/i/spaces/1dRJZEwjBAMGB

November 10th Session: https://twitter.com/i/spaces/1PlJQDwrWLNGE

Please join us.

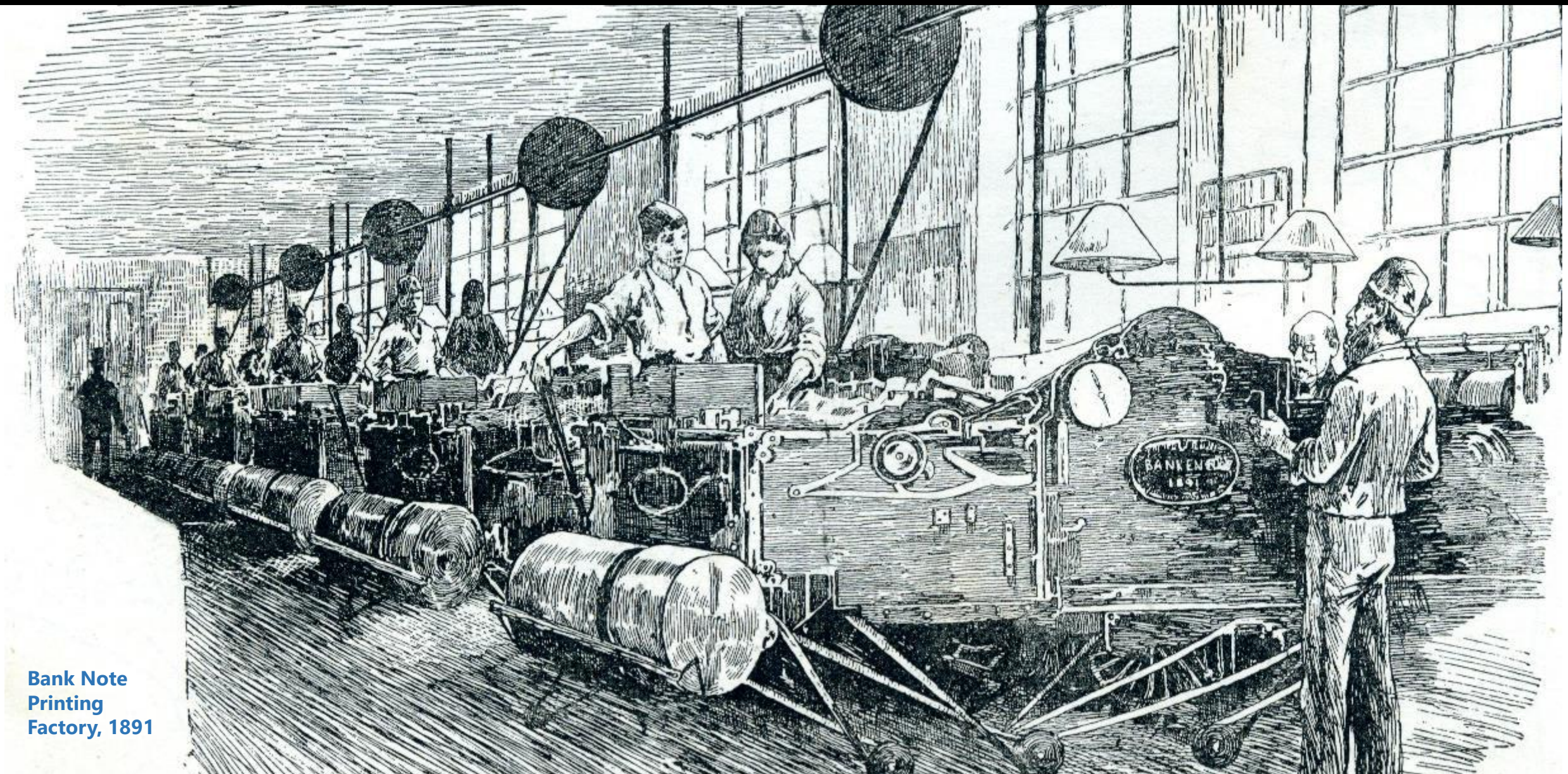
To Learn More
https://www.biotechhangout.com/

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

To meet with Stifel
yeungn@stifel.com

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

Macro Update



Bank Note Printing Factory, 1891

Fed Governor Michelle Bowman Comments on Inflation on November 7, 2023

Before I dig a bit deeper into these questions and we turn to our conversation, I'd like to offer a few thoughts on the economy and monetary policy. After sharply tightening monetary policy over the past year and a half to reduce inflation, at our November meeting, the Federal Open Market Committee (FOMC) voted to maintain the target range for the federal funds rate at 5-1/4 to 5-1/2 percent and continued the run off of the Fed's securities holdings.

We have seen considerable progress on lowering inflation, but inflation remains high and recent readings have been uneven. The latest personal consumption expenditure (PCE) inflation index data showed 12-month changes in total and core inflation of 3.4 percent and 3.7 percent, roughly similar to the previous month's reading. **However, some components of core services inflation have picked up, and I see a continued risk that core services inflation remains stubbornly persistent. In my view, there is also a risk that higher energy prices could reverse some of the progress made to bring overall inflation down.**

The economy has remained strong as the FOMC raised the federal funds rate, and recent data indicate that economic activity has accelerated with real gross domestic product (GDP) growing at a 4.9 percent annual rate in the third quarter. Consumer spending has also accelerated, and the housing sector appears to be continuing to rebound. The latest employment report showed a labor market with healthy job gains. Over the past year, labor force participation has improved with the average pace of job gains slowing somewhat, a sign that labor market supply and demand may be coming into better balance.

While I continue to expect that we will need to increase the federal funds rate further to bring inflation down to our 2 percent target in a timely way, I supported the FOMC's decision last week to hold the target range for the federal funds rate at the current level as we continue to assess incoming information and its implications for the outlook. Currently, the federal funds rate appears to be restrictive, and financial conditions have tightened since September. Some of this tightening has occurred through longer term bond yields, which can be volatile over time as conditions change. We don't yet know the effects of tightened financial conditions on economic activity and inflation. Moreover, there is an unusually high level of uncertainty regarding the economy and my own economic outlook, especially considering recent surprises in the data, data revisions, and ongoing geopolitical risks. But I will be closely watching the incoming data as I assess the implications for the economic outlook and the appropriate setting of monetary policy.

Michelle Bowman
Fed Governor

Source: https://www.federalreserve.gov/newsevents/speech/bowman20231107a.htm

Stocks Snap Winning Streak After Powell Warns Inflation Victory Not Assured

David Uberti, *Wall Street Journal*, November 9, 2023 (excerpt)

The S&P 500's shot at its longest winning streak since 2004 appeared within grasp for much of Thursday's trading session. Then Federal Reserve Chair Jerome Powell and the Treasury market crashed the party.

The S&P 500 finished 0.8% lower, thwarting what would have been just its 32nd nine-day winning streak since 1928, according to Dow Jones Market Data.

A 0.9% slip by the tech-heavy Nasdaq Composite ended a nine-day winning streak of its own. The Dow Jones Industrial Average fell 0.6%, or about 220 points.

Optimism flowed into the stock market after Powell last week said that an autumn run-up in Treasury yields could push up borrowing costs and potentially finish America's inflation fight without further rate hikes.

On Thursday, investors tapped the brakes after a government sale of $24 billion in long-term debt didn't entice as many buyers as anticipated. Benchmark 10-year yields, which offer practically risk-free returns, ticked higher afterward to 4.629%.

The resulting decline in stocks accelerated after Powell said at a conference in Washington that **it was too early to declare victory against price pressures. "Inflation has given us a few head fakes," he said. "If it becomes appropriate to tighten policy further, we will not hesitate to do so."**

Source: https://www.wsj.com/finance/stocks/global-stocks-markets-dow-news-11-09-2023-83062c11

One Fed Official is Now Worrying About Overshooting

Nick Timiraos, *Wall Street Journal*, Nov 9, 2023 (excerpt)

"A Federal Reserve official said the central bank will need to pay close attention to the effects of higher longer-term bond yields to make sure they don't slow the economy more than expected over the coming year.

Austan Goolsbee, president of the Federal Reserve Bank of Chicago, said in an interview Wednesday the recent run-up of longer-term borrowing costs could become more important as the central bank shifts its focus from how high to raise interest rates and toward how long to hold them near a 22-year high.

"The historical evidence suggests that long rates, even more than short rates, have a very substantial effect on real economic performance in a number of predictable areas—construction, investment, consumer durables," he said. "If that is sustained, the Fed will have to think about the tightening impact of those credit conditions on economic performance, and would there be dangers of overshooting."

Over the past two years, Fed officials raised rates at the most rapid pace in decades—most recently in July—to bring inflation under control. They have held rates steady since then, including at their meeting last week, as price pressures eased.

The Labor Department last week reported that the unemployment rate ticked up to 3.9% in October from 3.8% in September and from a recent low of 3.4% in April, a sign that demand for workers, while still strong, has eased in recent months."

Source: https://www.wsj.com/economy/central-banking/austan-goolsbee-says-fed-will-need-to-monitor-risks-of-overshooting-on-rates-9acab785

Moody's Changes Outlook on U.S. Ratings to Negative

Stephen Nakrosis, *Wall Street Journal*, Nov 10, 2023 (excerpt)

"Moody's Investors Service on Friday said it was revising the outlook on the U.S. government's ratings to negative, while affirming the long-term issuer and senior unsecured ratings at Aaa.

Moody's said a key driver to the outlook change was its assessment that downside risks to the nation's fiscal strength have increased "and may no longer be fully offset by the sovereign's unique credit strengths."

Given higher interest rates and without effective measures to reduce government spending or increase revenues, the agency said it expects fiscal deficits will remain very large and debt affordability would be significantly weakened.

The rise in Treasury bond yields has increased pre-existing pressure on debt affordability, Moody's said. It expects interest payments relative to revenue will rise to around 26% in 2033 from 9.7% in 2022. Additionally, Moody's said it sees interest payments relative to GDP will rise to around 4.5% in 2033, from 1.9% in 2022."

Source: https://www.wsj.com/finance/moodys-changes-outlook-on-u-s-ratings-to-negative-eb9ecad7

Biopharma Market Update

XBI Closed at 66.95 Last Week (Down 6.3%)

After a rare up week, the XBI headed down again last week. Members of the Fed gave neutral to positive comments. Biotech went down and the S&P 500 went up.

Biotech Stocks Down Last Week

Return: Nov 4 to Nov 10, 2023

Nasdaq Biotech Index: -4.3%
Arca XBI ETF: -6.3%
Stifel Global Biotech EV (adjusted): -8.8%*
S&P 500: +1.3%

Return: Jan 1 to Nov 10, 2023

Nasdaq Biotech Index: -11.8%
Arca XBI ETF: -19.3%
Stifel Global Biotech EV (adjusted): -13.2%*
S&P 500: +15.0%

Divergence starting to get really wide.

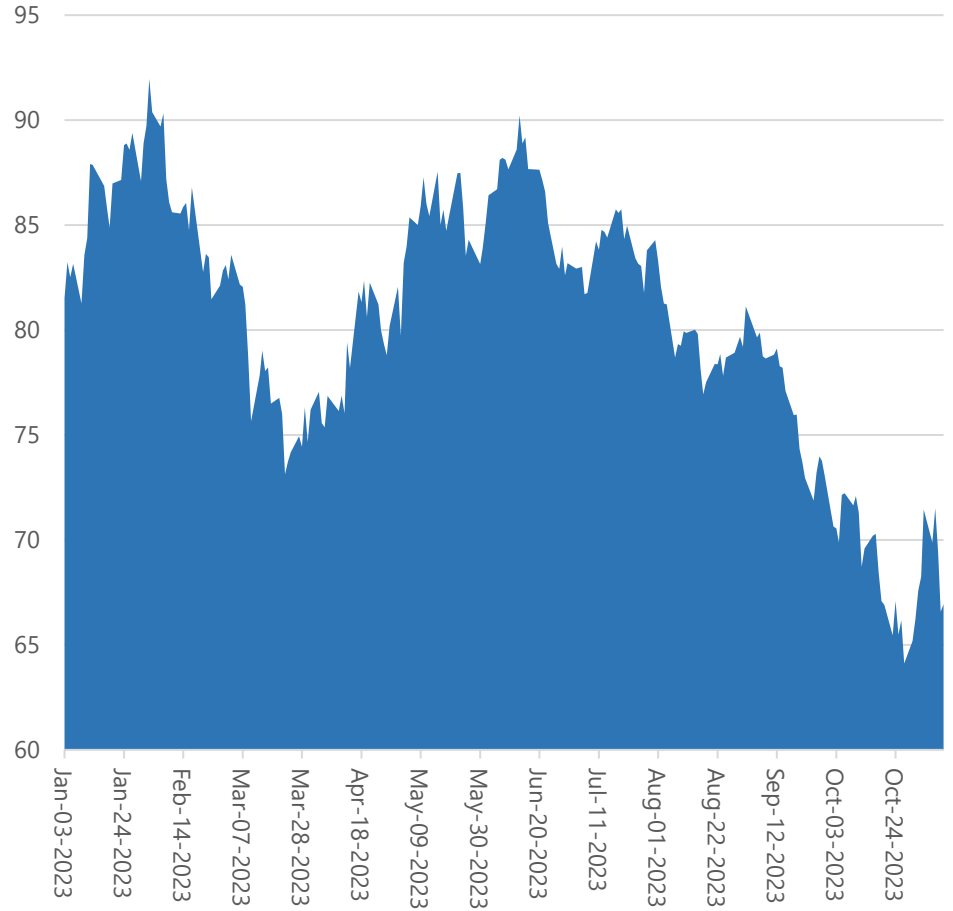
VIX Down

Oct 21: 29.7%
Jan 20: 19.9%
May 26: 18.0%
July 21: 13.6%
Sep 29: 17.3%
Oct 27: 21.2%
Nov 3: 15.2%
Nov 10: 14.2%

10-Year Treasury Yield Flat

Oct 21: 4.2%
Jan 20: 3.48%
May 26: 3.8%
July 21: 3.84%
Sep 29: 4.59%
Oct 27: 4.86%
Nov 3: 4.57%
Nov 10: 4.61%

VIX, Jan 1 to Nov 10, 2023

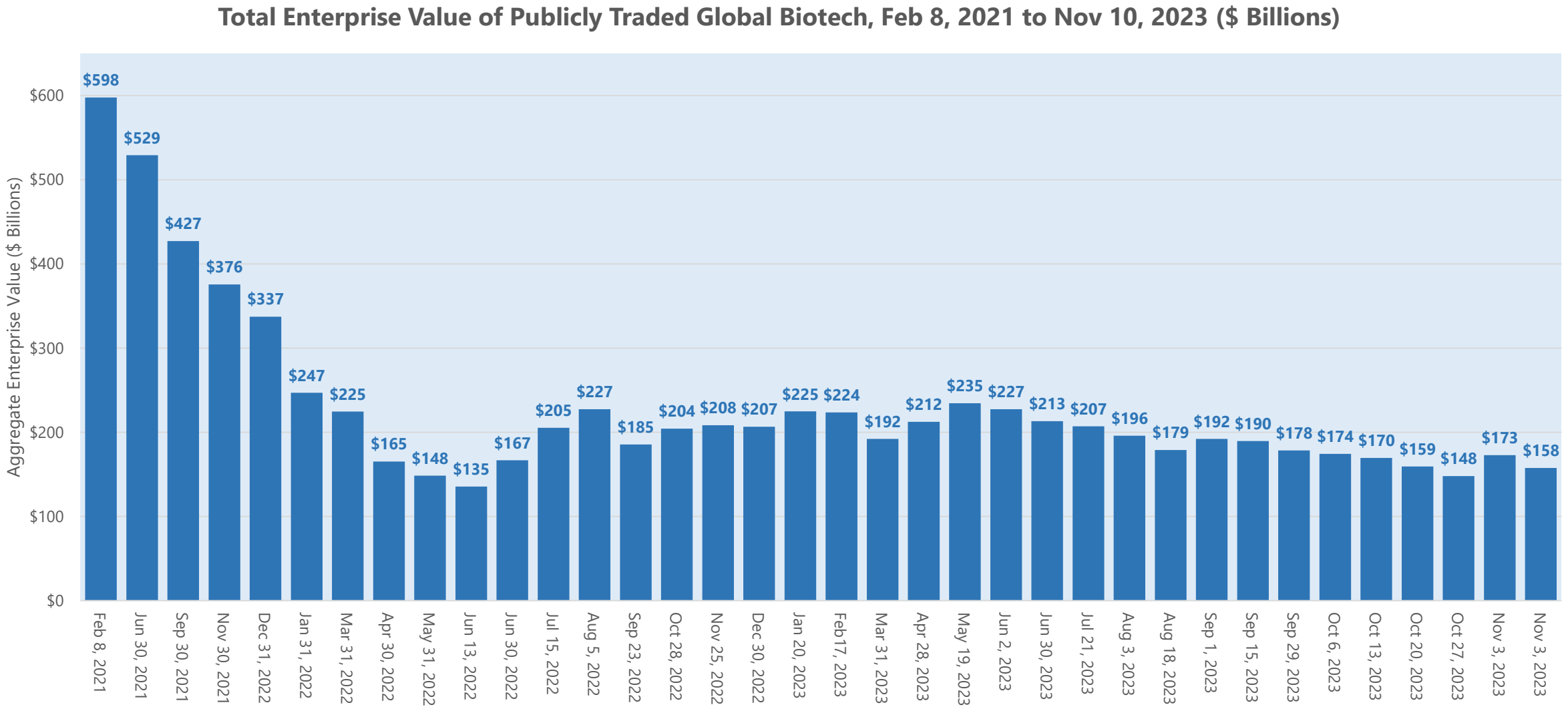


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Down Significantly Last Week

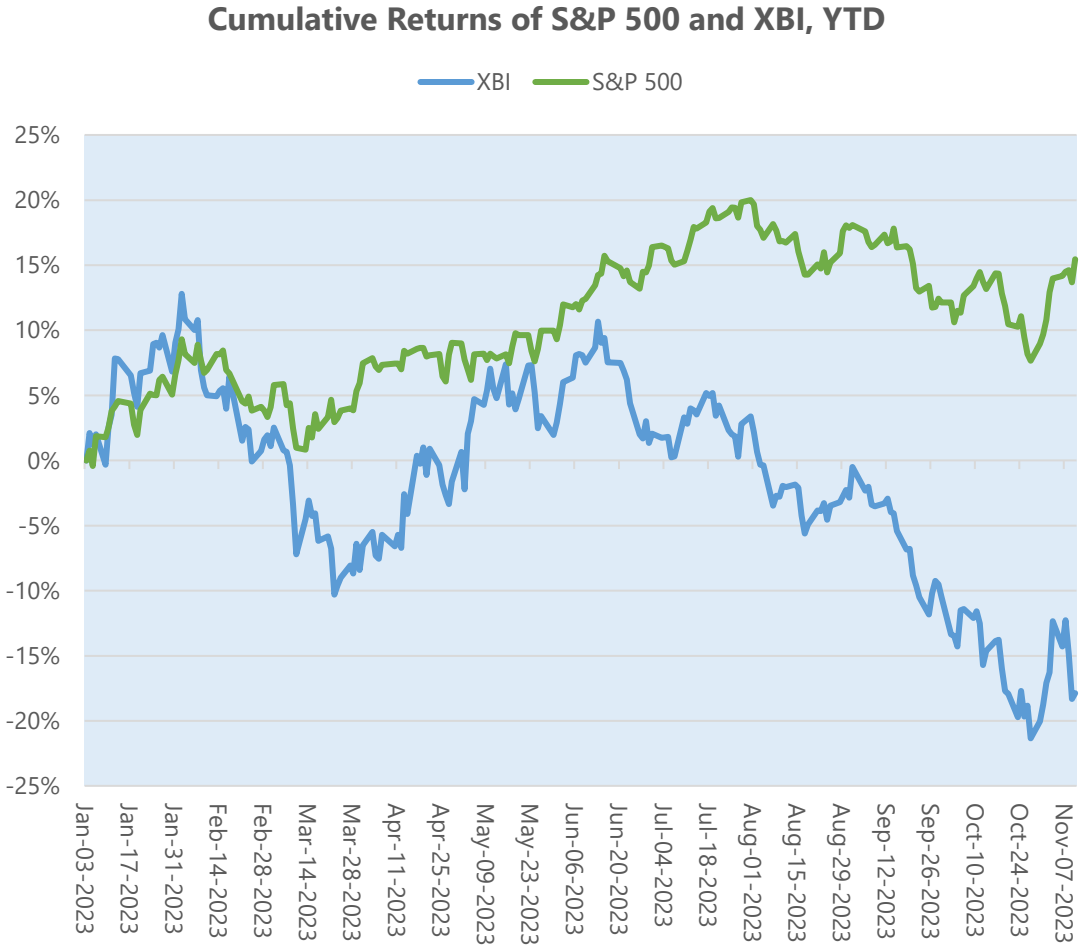
The total enterprise value of the global biotech sector fell by 8.8% last week and is now down over 13.2% for the year after adjusting out for exits and entries (versus 5.8% last week)

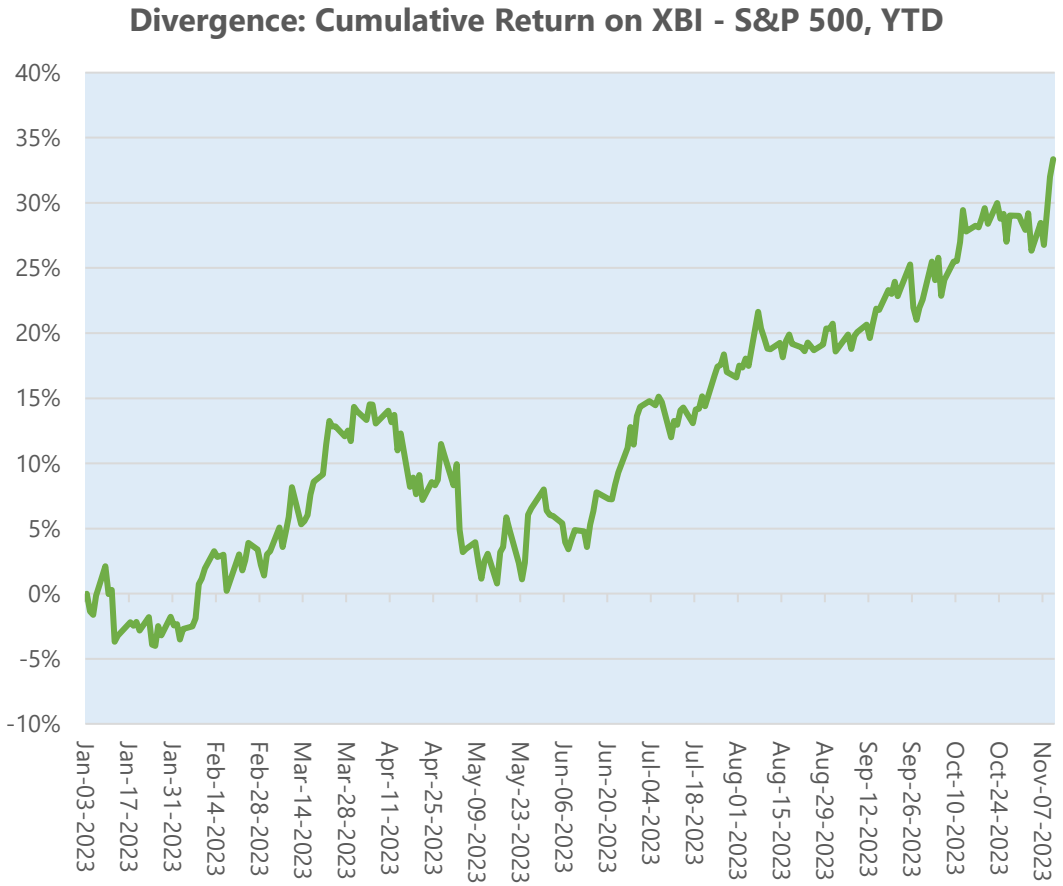


Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Last week included a removal of a commercial company with a $7bn value.

S&P - XBI Divergence Getting Really Wide

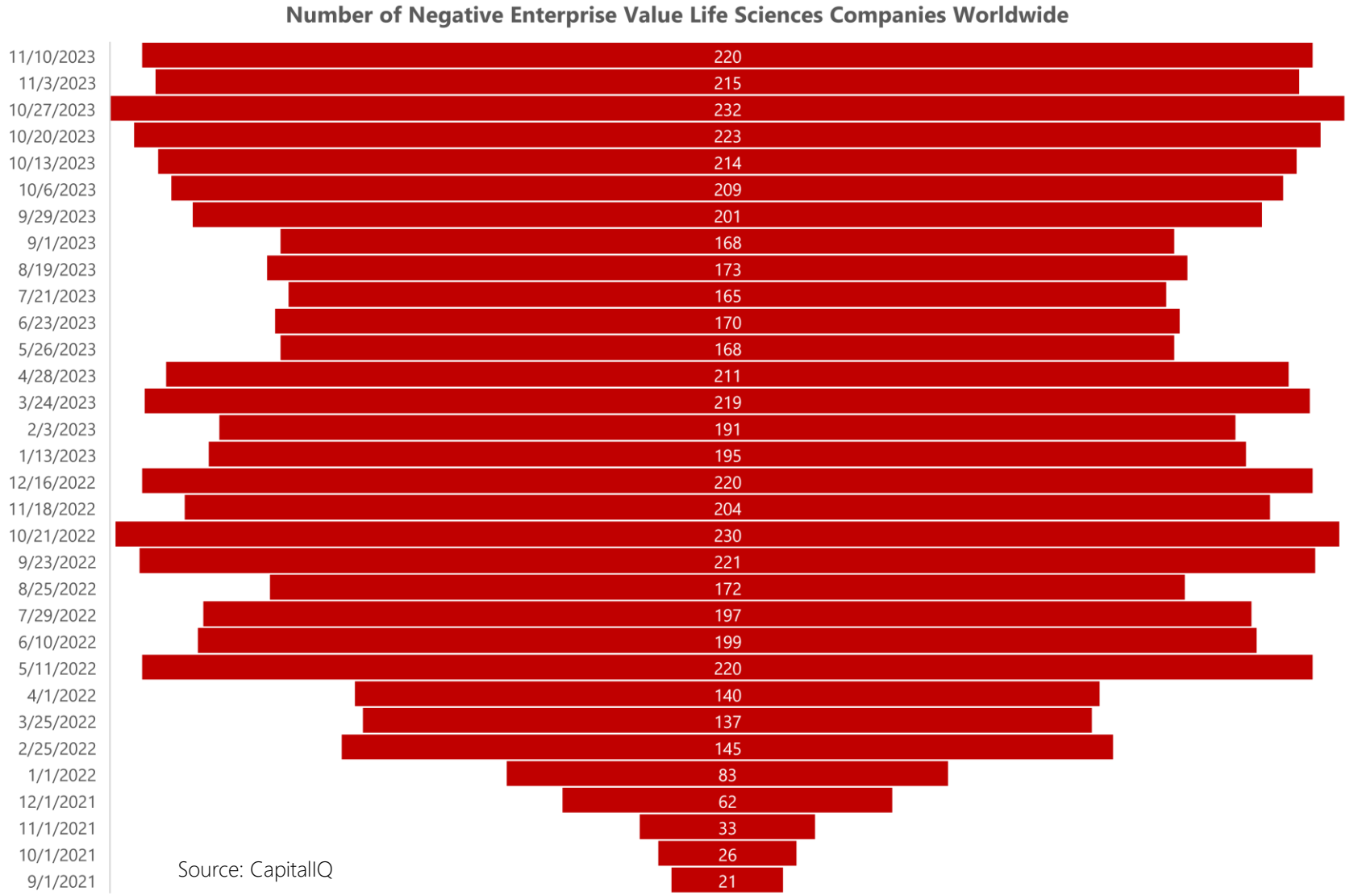
The spread in performance between the S&P 500 and the XBI widened by seven points last week to 34 percentage points. We believe that this presages a biotech rally. Large cap generalists understand that rates have peaked, and this is positive. In contrast, the biotech sector, to a significant extent, remains a fear driven market that has yet to adapt to the emerging reality of a more dovish Federal Reserve.





Source: CapitalIQ.

Number of Negative Enterprise Value Life Sciences Companies Rose to 220 in Last Week



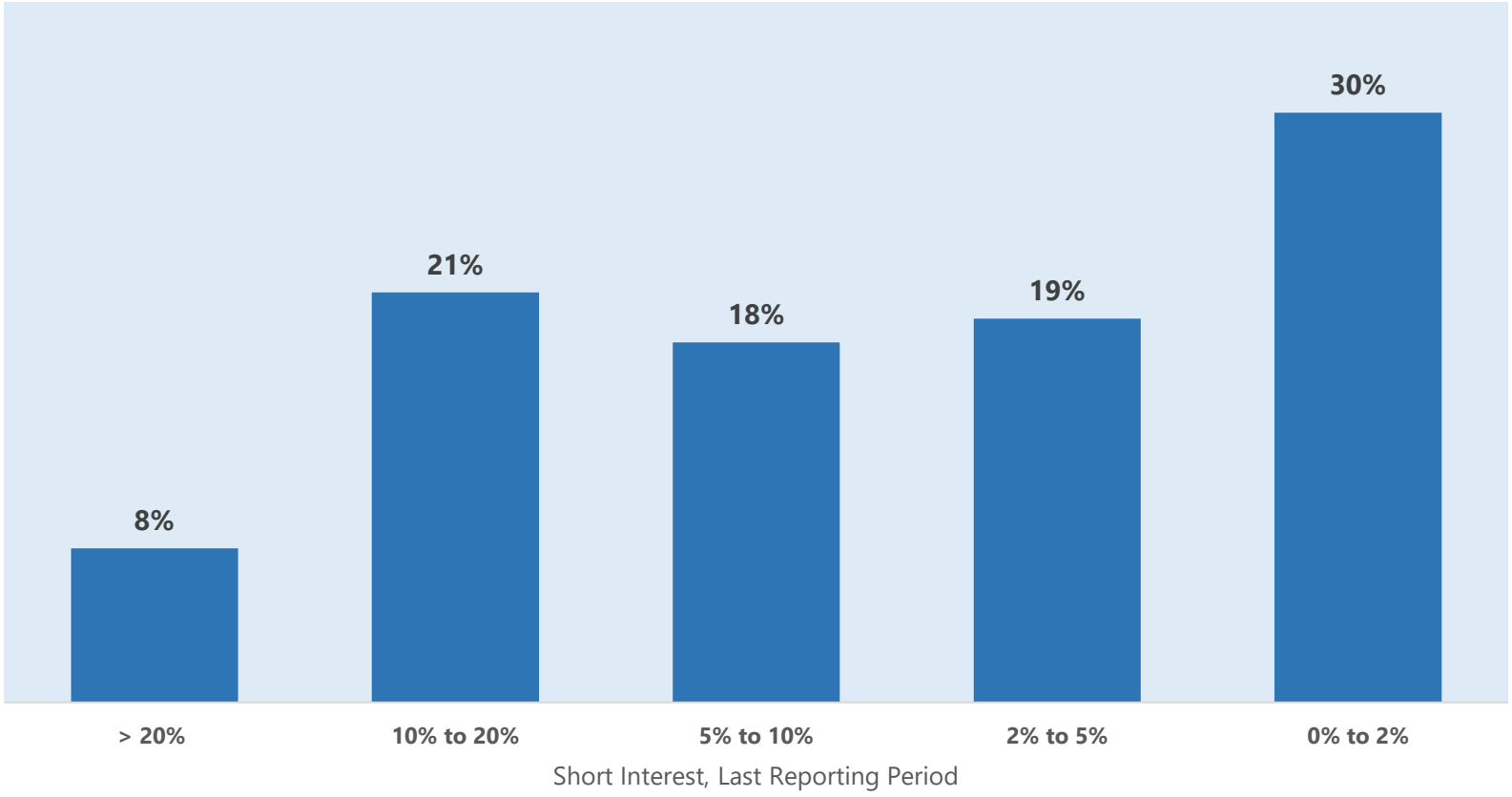
Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 215 a week ago to 220 last Friday.

Stocks with High Short Interest Did Not Do Well Last Week

It looks like short sellers took advantage of the lack of good news to re-enter heavily shorted stocks after the previous week's covering rally. Only one stock with over 20% short interest rose in value last week (Novavax). In contrast, heavily shorted names like Allogene, Emergent, Cassava and bluebird were all down 10% or more last week.

Percent of Life Sciences Stocks That Rose in Value Last Week by Short Interest (Short Interest Last Reporting Period, N=778)



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

Life Sciences Sector Down 1.2% Last Week

Last week saw a 1.2% decline in life sciences stocks worldwide. The sector's value dropped by $103 billion. Biotech stocks were down the most. Pharma services, CDMOs and API shares were up last week.

Sector	Firm Count	Enterprise Value (Nov 10, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,882	3.0%	1.1%	-1.6%
Biotech	812	$158,023	-8.8%	0.4%	-5.1%
CDMO	40	$149,396	1.1%	-8.0%	-18.1%
Diagnostics	83	$229,952	-1.7%	3.3%	-12.7%
OTC	31	$27,599	-0.6%	-3.1%	-1.8%
Pharma	724	$5,592,059	-0.7%	-4.7%	-0.3%
Pharma Services	40	$200,238	0.9%	-0.9%	-2.1%
Tools	53	$581,997	-1.5%	-6.8%	-24.8%
Devices	181	$1,427,453	-2.7%	-0.7%	-8.4%
HCIT	11	$20,850	-1.9%	-9.8%	-24.6%
Total	**2056**	**$8,469,450**	**-1.2%**	**-3.8%**	**-5.0%**

Source: CapitalIQ

The Biotech Bear Market, Fear and the Future

Biotech, Fear and the Future

We'll be the first to say it. Right now, investor sentiment in the biotech market is terrible.

We're not sure we've ever seen worse.

We are three years into a brutal biotech bear market. The XBI is down 70% from peak and doesn't seem to be improving.

There is a steady stream of positive sector fundamentals: translational breakthroughs in genetic disease, heart disease, obesity, liver disease and neuroscience. What we can do today with gene editing and RNA boggles the mind.

And no one seems to care.

In the markets, that is.

To be clear, the biotech stocks markets typically feature a richly diverse set of investors – retail, science-oriented specialists, hedge funds, generalist long funds, sovereign funds and the like.

If anything, these groups are currently *leaving* the market. There *are* specialist funds that are in real trouble at this point.

It's completely understandable that the market is in shambles. We had way too many companies enter the market with a business plan based on hope.

Too many investors have been focused on proximal events rather than the real prospects of a company's business plan.

We are in the depths of a 3-year bear market in biotech

Fear and the Future (cont.)

When you see 200+ companies trading below cash, one has to wonder if our sector might benefit from a mass lecture on corporate governance given to boards on the one hand and valuation basics given to investors on the other.

A negative enterprise value problem can be solved in five minutes with a special dividend or a stock buyback.

Too many companies hold on to non-financeable business plans to the bloody end. Boards say “never, ever give back the cash.”

And investors know it. There are clearly some **structural issues** in the sector.

Those of you who are masochistic enough to read our reports week after week will have noted a conspicuous lack of optimism in recent months.

No green shoots.

Instead, parched desert. Storm clouds. Gloom. That sort of thing.

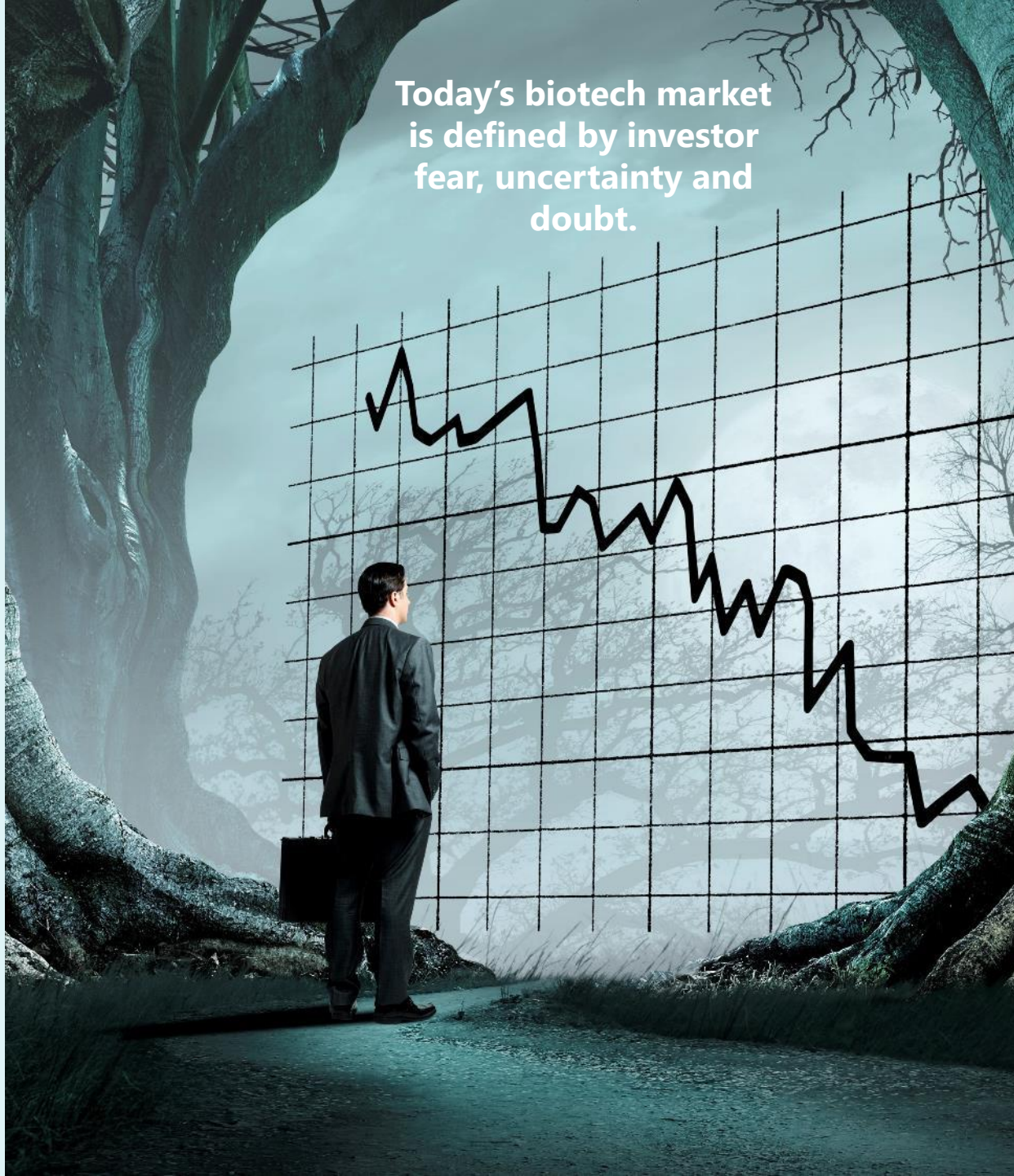
We noted that the vigorous market rally in the week of Oct 30 was mainly caused by short covering rather than fundamental buying.

The proverbial **dead cat bounce**.

We do think it’s time for a **rally** to hit the sector.

The comment seems out of place. We know.

Hard to imagine in a way.



Fear and the Future (cont)

For now, the market is possessed by fear and some anger.

Not fundamentals.

To give one illustration, we admired last week's move by **Ventyx** to come out and say that their TYK2 inhibitor clearly didn't work well enough in psoriasis and that they would discontinue development and continue elsewhere. The company gave investors a highly detailed presentation on their clinical findings.

Ventyx shares were **pulverized** on the news (down 87% for the month) and are trading at half of cash in the bank. The tricky thing is that the company has two other highly interesting programs.

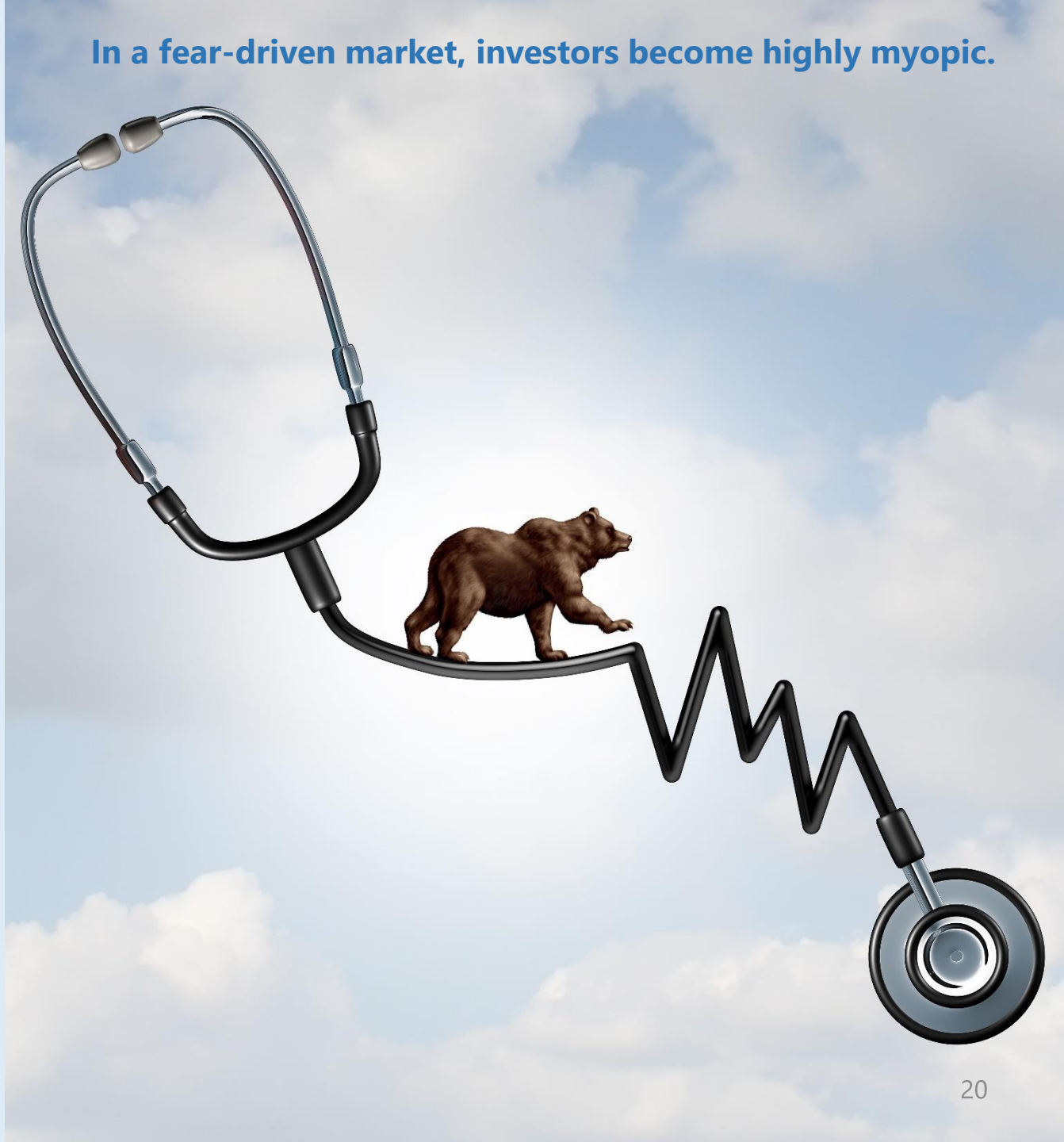
In the clinic.

Investors in today's market **shoot first and ask questions later**.

No one is waiting around to figure out how that NLRP3 program is being tested and what is might do.

A fear driven market induces a type of **extreme myopia**: Find "conviction bets" and hope that they work out. Sell immediately if they don't. Ignore everything else.

To give another illustration, last week saw **Pyxis Oncology** announce a 40% headcount reduction and a refocusing effort. They indicating that they would be going forward with two programs, led by a Phase 1 ADC targeting EDB-fibronectin. This program has a good chance of working and will have data in the next six months. Dosing is well underway.



Fear and the Future (cont.)

As of its last reporting period, Pyxis had $133 million in the bank and does not appear to be prone to irresponsible spend. Management is experienced and determined to build something real in the ADC field.

Pyxis stock went *down* on news of a restructuring and focusing.

To state the obvious, the market's actions make little sense when viewed through the lens of rationality.

On the other hand, they make great sense when viewed through the lens of myopia and fear.

This time of the year features no shortage of conferences, conversations and panels on the market.

A widely expressed view is that **2023 is done for**. Funds have closed shop and will be coming back into the market in 2024.

Don't expect anything to happen between now and JPM.

Maybe some champagne bubbles amidst and parties featuring **holiday sweaters** that would be best kept hidden in the attic.

This makes perfect sense in a way.

Redemptions will come next year and it's going to be hard to explain away three years of negative returns. If you did "OK" in your fund this year, you might as well fold up the tent and hope that you don't get too many redemptions from your Limited Partners at the start of 2024.

Last week's moves would suggest that this market is not well.

Fear and the Future (cont.)

But this logic misses a bunch of key points: (1) there is a huge amount of **cash on the sidelines**, (2) the bargains are really good *now,* (3) funds that are way down might as well take some chances, (4) short interest remains high and (5) alternative sources of liquidity are popping up everywhere.

If you will, there is **dry tinder** out there that favors a rapid bull market in biotech.

You don't want to be a fund manager that misses a big rally.

The high short interest and cash positions create particularly strong conditions for a vigorous market recovery. Some call this type of scenario a "melt up".

If the XBI jumps 20% (which isn't that much, really, given how far down it has come), we think confidence would start to return. Generalists would start to look again. Companies with great stories would start to recover etc.

This will all take time, of course. We can't tell you if this scenario plays out next week or next month. But the conditions for a strong market rally are in place.

We do *not* think that the next six weeks will be **quiescent.**

As noted on the following page, a key factor is this week's **upcoming inflation data**. Should the data be as expected, or better, we do think we start to see more and more buying in the market.

The Fed remains vigilant but has clearly signaled a view that rates are plenty high and its now time for the effect of tightening to take place.

The weak employment numbers a few weeks back were a good start.

Let's see how this all plays out.

Is the Stock Market Rally About to Rev Up?

Gunjan Banerji, Wall Street Journal, Nov 12, 2023 (excerpt)

FOMO ("fear of missing out") in the stock market is back.

A lightning-fast rebound has driven the S&P 500 up in nine of the past 10 sessions and 7.2% over the past two weeks, the best such stretch of the year. Now, many investors are betting the rally has legs.

Some have piled into funds tracking U.S. stocks, while others have abandoned trades that would profit in times of market turmoil. Many have slashed bearish wagers against the S&P 500 and tech-heavy Nasdaq-100 index, fearful of getting caught flat-footed if the big gains continue.

The Cboe Volatility Index, or VIX, known as Wall Street's "fear gauge," has plunged from its October highs, and recently slid for eight consecutive sessions. It is a sign that traders are abandoning insurance-like contracts that would protect them from a stock swoon in coming weeks, or expecting markets to stay placid.

"People are trying to position for a year-end rally at this point," said Zhiwei Ren, a portfolio manager at Penn Mutual Asset Management.

Ren said he took a cautious stance in markets for much of this year, concerned that a recession was right around the corner. The market advance has pushed him to rethink his approach. Recently, he scooped up some bullish bets tied to the S&P 500 in the options market to profit from any bigger gains that might come through the end of the year. Activity in such options hit one of the highest levels on record in November.

Behind the market's U-turn? Stocks and bonds got a double boost from Washington earlier this month. The Treasury increased the size of longer-term debt auctions by a smaller amount than many had expected, and the Federal Reserve hinted that it likely won't raise interest rates again this year.

Government bond yields, which have stirred much of the recent volatility, dropped after breaching 5% for the first time in 16 years in October, giving ammunition to the stock bulls. The S&P 500 is sitting on gains of 15% for 2023, while the Nasdaq Composite is up 32% after notching its best day since May on Friday.

In the coming days, investors will parse the latest round of inflation data when the consumer-price index and producer-price index figures are released on Tuesday and Wednesday.

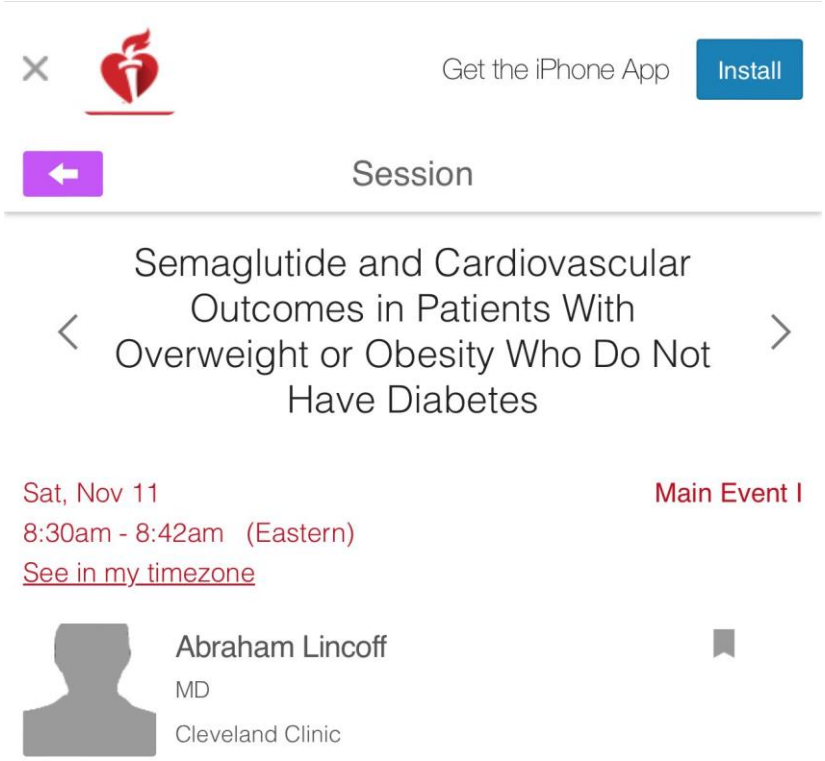
With just a few weeks left of 2023, the doomsday forecasts on the economy that Wall Street entered the year with don't seem to be panning out.

Charles Shriver, a portfolio manager at T. Rowe Price who oversees about $50 billion in assets, said he kept a sizable chunk of his portfolios in cash for much of the year and took advantage of the October market swoon to pour some of it into equities. He says he expects stocks to keep rising.

"We would look for opportunities to add to equities," Shriver said.

Source: https://www.wsj.com/finance/stocks/is-the-stock-market-rally-about-to-rev-up-3508d6ef

Novo Nordisk SELECT Data at AHA



Abraham Michael Lincoff; Kirstine Brown-Frandsen, Cleveland Clinic, Cleveland, OH; Helen M Colhoun, Novo Nordisk A/S, Søborg, Denmark; John Deanfield, University of Edinburgh, Edinburgh, United Kingdom; Scott S Emerson, University College London, London, United Kingdom; Sille Esbjerg, University of Washington, Seattle, WA; Søren Hardt-Lindberg; G. Kees Hovingh; Steven E Kahn, Novo Nordisk A/S, Søborg, Denmark; Robert F Kushner, VA Puget Sound Health Care System and University of Washington, Seattle, WA; Ildiko Lingvay, Northwestern University, Chicago, IL; Tugce Kalayci

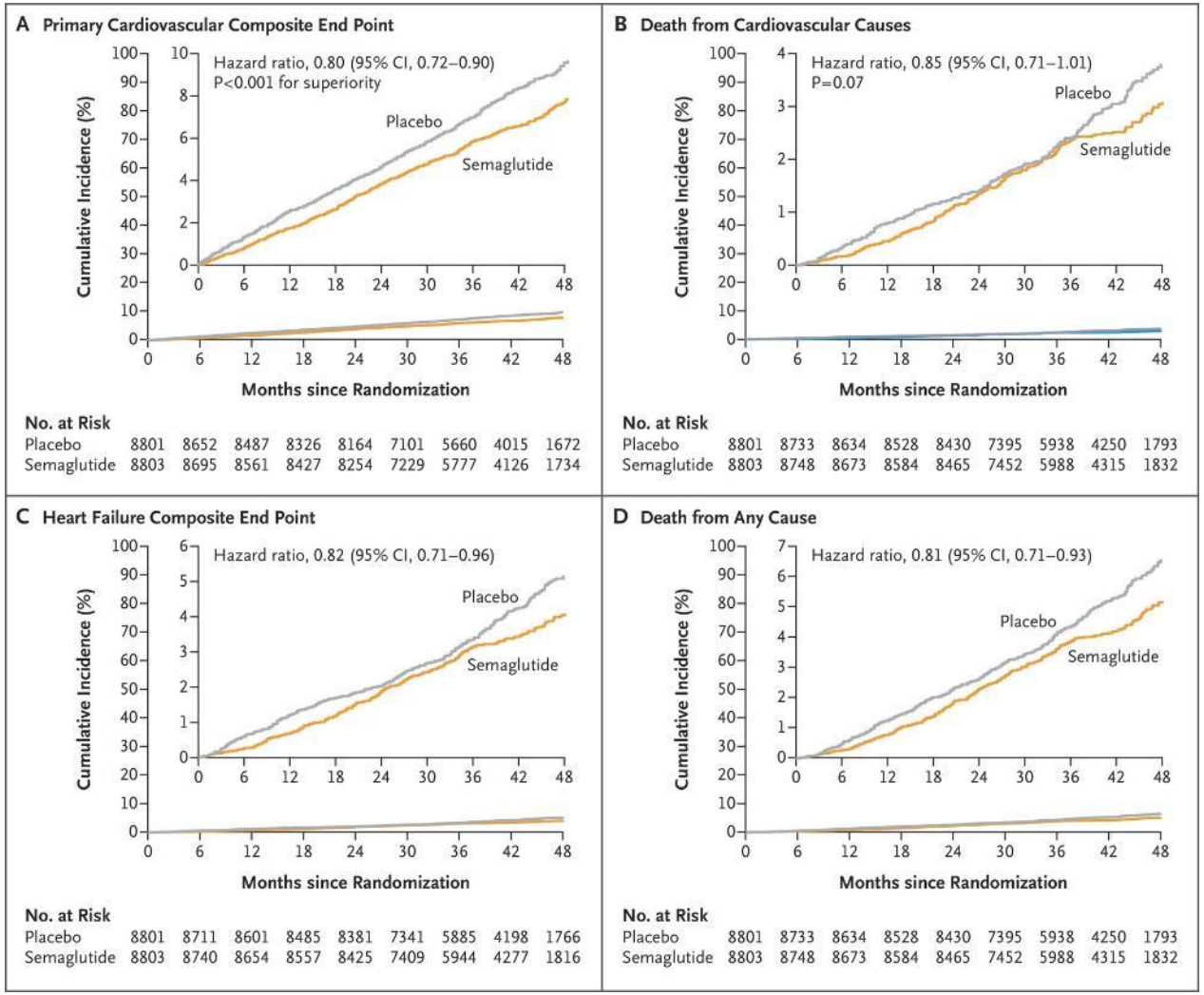
SELECT Data from Novo Nordisk

An AHA session last Saturday morning was devoted to the SELECT trial of semaglutide (Wegovy; Novo Nordisk) in patients who had a history of cardiac problems and were overweight.

Top-line results for this international trial of more than 17,000 subjects have already been released, showing that a once-a-week, subcutaneous, 2.4-mg dose of the glucagon-like peptide-1 (GLP-1) receptor agonist lowers body weight along with adverse cardiovascular events by 20%.

The AHA event was accompanied by simultaneous publication of the SELECT results in the *New England Journal of Medicine*.

SELECT Data from Novo Nordisk



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

Panel A shows the cumulative incidence of the primary cardiovascular composite end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). Panel B shows the cumulative incidence of the first confirmatory secondary end point (death from cardiovascular causes). Panel C shows the cumulative incidence of the second confirmatory secondary end point (heart failure composite end point: death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure). Panel D shows the cumulative incidence of the third confirmatory secondary end point (death from any cause). The definitions of all end points are provided in the Supplementary Appendix. Cumulative incidence was estimated with the use of the Aalen–Johansen method with accounting for competing risk, and hazard ratios were estimated with the Cox proportional hazards regression model. Because the between-group difference in death from cardiovascular causes did not meet the required P value for hierarchical testing, results for the two subsequent end points in the testing hierarchy are reported as point estimates and 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for these secondary end points. The insets show the same data on an enlarged y axis. The x axis is truncated at 48 months because of the limited number of patients in the trial after 48 months.

Impressive Reduction in Risk of Pre-Diabetes

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., et al., for the SELECT Trial Investigators*

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Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

* Plus–minus values are means ±SE. Data are from the full analysis population. The binary end points were analyzed by logistic regression with treatment as factor and the baseline glycated hemoglobin level as a covariate. The continuous end points assessing changes from randomization to week 104 were analyzed with the use of analysis of covariance with treatment as factor and the baseline value as a covariate, with multiple imputation for missing values under a missing-at-random assumption. High-sensitivity CRP, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were log-transformed before analysis, and the results are thus reported as relative changes (i.e., percentage changes). Because supportive secondary end points were not corrected for multiplicity, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for supportive secondary end points. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.929 and subtract 2.15.

The reduction in glycated hemoglobin levels in obese patients without diabetes, was highly significant.

Very impressive result.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

Big Reduction Seen in CRP

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Medications in the GLP-1 receptor agonist class have been shown in animals with or without diabetes to reduce inflammation, improve endothelial and left ventricular function, promote plaque stability, and decrease platelet aggregation. In this trial, semaglutide was associated with changes in multiple biomarkers of cardiovascular risk, including blood pressure, waist circumference, glycemic control, nephropathy, and levels of lipids and C-reactive protein. For perspective, the observed decrease of 3.3 mm Hg in systolic blood pressure in this trial is greater than the decrease of 2 mm Hg predicted by a meta-analysis to yield a 7% reduction in vascular mortality, and the 37.8-percentage-point decrease in the high-sensitivity C-reactive protein level with semaglutide in this trial is similar to that reported with statins. These changes in cardiovascular biomarkers are notable for having been achieved on a background of high rates of use of statins, antihypertensive agents, and other evidence-based medications for atherosclerotic disease. Although our understanding of the mechanisms of cardiovascular protection with semaglutide remains speculative, the consistent effects on cardiometabolic risk factors support the hypothesis that clinical benefit is achieved through multiple interrelated pathways.

Statins knock down CRP, a measure of activation of innate inflammatory pathways by around 35%. It's remarkable that adding semaglutide *on top* of statins buys an additional 37.7% reduction. There are a number of medications in development for inflammation control (e.g., see Ventyx discussion of NLRP3's elsewhere in this deck). In the same sense that a GLP-1 agonist may reduce the need for an FGF21 for NASH, we may see less value for a number of medicines in development for inflammation (e.g., NLRP3's, MK2's etc).

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

Study Included Well Treated Patients

- Patients in SELECT Trial were well treated for CV risk:
  - 87.7% on statins
  - 86.5% on PAIs (platelet aggregation inhibitors)
  - Most on drugs for hypertension
- Patients were in decent shape
  - Average pulse of 69
  - Average LDL of 78
- And, yet, still benefitted quite substantially from weight loss.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

CV medications – no. (%)		
Platelet aggregation inhibitors	7,612 (86.5)	7,569 (86.0)
Acetylsalicylic acid	6,909 (78.5)	6860 (77.9)
P2Y12 receptor inhibitors	2,925 (33.2)	2,998 (34.1)
Other	77 (0.9)	104 (1.2)
Anti-thrombotic medications	1,086 (12.3)	1,150 (13.1)
Vitamin K antagonists	336 (3.8)	340 (3.9)
Direct oral anticoagulants	738 (8.4)	784 (8.9)
Lipid-lowering drugs	7,928 (90.1)	7,929 (90.1)
Statins	7,716 (87.7)	7,709 (87.6)
Ezetimibe	1,188 (13.5)	1,144 (13.0)
Fibrates	213 (2.4)	266 (3.0)
PCSK-9 inhibitors	177 (2.0)	162 (1.8)
Beta blockers	6,182 (70.2)	6,175 (70.2)
Angiotensin-converting-enzyme inhibitors	3,963 (45.0)	3,966 (45.1)
Angiotensin-receptor blockers	2,618 (29.7)	2,569 (29.2)
Calcium channel blockers	2,407 (27.3)	2,331 (26.5)
eGFR – mean mL/min/1.73 m^2	82.4 ± 17.5	82.5 ± 17.3
UACR – mg/g – median (IQR)	7.4 (4.5 to 15.7)	7.3 (4.5 to 15.1)
Lipids – mg/dL – median (IQR)		
Total cholesterol	153 (131 to 182)	153 (131 to 183)
HDL cholesterol	44 (37 to 52)	44 (37 to 52)
LDL cholesterol	78 (61 to 102)	78 (61 to 102)
Triglycerides	134 (99 to 188)	135 (100 to 190)
Systolic blood pressure – mmHg	131.0 ± 15.6	130.9 ± 15.3
Diastolic blood pressure – mmHg	79.4 ± 10.0	79.2 ± 9.9
Pulse – bpm	68.9 ± 10.6	68.6 ± 10.7
EQ-5D-5L index score	0.88 ± 0.15	0.88 ± 0.15
EQ-5D-VAS score	77.15 ± 15.63	77.15 ± 15.73

To convert the values for HDL cholesterol and LDL cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for HbA_{1c} to millimoles per mole, multiply by 10.929 and subtract 2.15.

The category "Other" for the CV inclusion criteria includes patients for whom it is unknown if the patient fulfilled only one or several criteria and patients who were randomized in error and did not fulfil any criteria.

*Plus–minus values are means ± SD.

†Race and ethnic group were reported by the patients. Race was not reported for 95 patients (1.1%) in the semaglutide group and 74 patients (0.8%) in the placebo group. The category "Other" for race includes patients whose race was recorded as "American Indian or Alaska Native," "Native Hawaiian or Pacific Islander," or "Other". Ethnicity was not reported for 95 patients (1.1%) in the semaglutide group and 76 patients (0.9%) in the placebo group.

‡The BMI is the weight in kilograms divided by the square of the height in meters.

BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; EQ-5D-5L, EuroQol-5 dimension-5 level; EQ-5D-VAS, EuroQol-5 dimension-visual analog scale; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density

Very Interesting Findings in AE Tables of SELECT Study

Table S3. Expanded Listing of Investigator-Reported Adverse Events.*

Event	Semaglutide (N=8,803)	Placebo (N=8,801)	P value
	Number of patients (percentage)		
Serious adverse events*,†	2,941 (33.4)	3,204 (36.4)	<0.001
Cardiac disorders	1,008 (11.5)	1,184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Injury, poisoning, and procedural complications	305 (3.5)	313 (3.6)	0.74
General disorders and administration-site conditions	273 (3.1)	316 (3.6)	0.07
Musculoskeletal and connective tissue disorders	236 (2.7)	254 (2.9)	0.41
Vascular disorders	231 (2.6)	259 (2.9)	0.20
Renal and urinary disorders	192 (2.2)	198 (2.2)	0.76
Respiratory, thoracic, and mediastinal disorders	180 (2.0)	276 (3.1)	<0.001
Hepatobiliary disorders	126 (1.4)	105 (1.2)	0.19
Blood and lymphatic system disorders	83 (0.9)	62 (0.7)	0.10
Metabolism and nutrition disorders	67 (0.8)	76 (0.9)	0.45
Reproductive system and breast disorders	65 (0.7)	43 (0.5)	0.04
Psychiatric disorders	59 (0.7)	49 (0.6)	0.39
Eye disorders	41 (0.5)	41 (0.5)	1.00
Investigations	34 (0.4)	41 (0.5)	0.42
Ear and labyrinth disorders	27 (0.3)	16 (0.2)	0.13
Endocrine disorders	19 (0.2)	20 (0.2)	0.87
Skin and subcutaneous tissue disorders	19 (0.2)	20 (0.2)	0.87
Congenital, familial, and genetic disorders	12 (0.1)	9 (0.1)	0.66
Product issues	11 (0.1)	16 (0.2)	0.34
Immune system disorders	11 (0.1)	14 (0.2)	0.56

Obese patients on Semaglutide were less likely to suffer from infection, nervous system disorders or respiratory disorders.

They were also less likely to get a surgical procedure.

The biggest effect size was for respiratory disorders.

And, as highlighted in blue, were not more likely to get cancer (and were less likely to discontinue the study because of cancer).

This all played out in just three years.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2307563

Eric Topol View of the SELECT Data

The good major findings

1. Semaglutide did reduce major events in this high-risk population by 20% and would be considered the first drug directed at obesity to have achieved this goal.
2. The 40-month follow-up is the longest thus far for a large trial of semaglutide vs placebo, which gives some confirmation of safety for this duration of therapy.
3. There was a consistent ~20% reduction across the different endpoints, although the time seen for divergence of the cardiovascular death curves or death from any cause (graphs below) was delayed > 3 years, in comparison to early separation fo the curves for non-fatal endpoints (mainly heart attack reduction).
4. As might be expected, the reduction of progression to diabetes was striking: only 3.5% progressed to HbA1c > 6.5% in the semaglutide group as compared with 12% in the placebo group, a 73% reduction. Along with this there was a fairly pronounced reduction of the C-reactive protein inflammatory marker 39% vs 3% reduced, for semaglutide vs placebo, respectively.
5. The findings were independent of overweight/obesity category at baseline, as seen in this subgroup analysis for the primary endpoint. In fact, the subgroups < 30 and 30-35 BMI demonstrated the most relative reduction.

Not so good findings

1. The *absolute reduction of the primary endpoint is only 1.5 per 100 people* treated, with the people in the trial representing a very high-risk cohort. And they had to be treated for 3+ years to derive that small absolute benefit. Note that the *price of Wegovy in the United States is $1,349 per month*.
2. The body weight loss achieved was only 8.5%. As I reviewed last December, this is considerably less than was seen in the Wegovy and Mounjaro previous, smaller randomized trials with less follow-up time (<1.5 years). It remains to be seen whether more extensive weight loss would further reduce cardiovascular events, and to what degree was the weight loss per se affecting the outcome improvement or driven in part by other effects of the drug, such as reduction of inflammation.
3. There is no exit strategy. Beyond losing weight, we know that people on these drugs lose muscle mass (not measured in the trial) and bone density, and the companies marketing these drugs have done nothing to assess strategies of weaning and discontinuation of the drugs to avoid these untoward effects, no less others that may crop up after extended (multi-year) exposure.

Eric Topol is a well-known American cardiologist, scientist, and author. He is the founder and director of the Scripps Research Translational Institute and a professor of Molecular Medicine and Executive Vice-President at Scripps Research Institute.

Source: https://erictopol.substack.com/p/the-big-trial-of-a-glp-1-drug-wegovy

Further Views on the SELECT Data

This is no ordinary conference presentation to think about. The reason is that the SELECT data represent the first time we have seen three plus years of exposure of a GLP-1 in more than 10,000 study participants. Compare, for example, to Lilly's SURMOUNT1 study, which looked at tirzepatide for 72 weeks in 2,539 obese persons.

Because the GLP-1 class is likely to become one of the most widely used drug classes in history (with record sales to boot), this look at safety and efficacy is very important.

We are highly impressed by the investment that Novo Nordisk made in sponsoring the study. With normal patient enrollment costs, their spend must have exceeded $1 billion. That is no small amount. Kudos to them!

We think the most important finding of the study is that of safety. With over 40,000 patient years of exposure, the fact that all-cause mortality *decreased* meaningfully on semaglutide is important and should give comfort to physicians who are contemplating long-term use of GLP-1's on their patients.

For those that would say that the CV event and mortality reduction is not all that big, we would note that the reduction percentagewise was quite large – and *on top* of the current standard of care. Further, three or four years is not that long of a time. The benefits of weight loss continue for many years after and have been documented in other large longitudinal studies of weight loss interventions.*

There are obviously some important questions that are raised by the study including the lower benefit seen in North American populations. Why is this?

The big question that strikes us looking through the *NEJM* paper is whether there would be a way to take a *precision approach* to the use of GLP-1's. This is obviously relevant given the cost of the medications. That is, are there specific patient populations that would benefit from the medications? For example, persons with very high obesity seemed to benefit less. That was a bit surprising (although presumably those persons didn't get anywhere near normal weight during the study).

Are their characteristics of patients that are associated with higher weight loss benefit? For example, Sam Klein of Wash U, St. Louis has argued that there is such a thing as a healthy obese person and that the real issue isn't obesity *per se* but insulin insensitivity (which is often induced by obesity).** He has demonstrated that there are plenty of metabolically healthy obese people who remain insulin sensitive and retain normal lipid levels. While the subjects in the SELECT study had to have had a history of cardiac disease it would be interesting to see if baseline metabolic characteristics such as insulin sensitivity, and triglyceride levels were related to outcomes after treatment in the study.

* See, for example, Kritchevsky et.al., (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4368053/

** See, for example, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4319438/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6763224/

Views on the SELECT Data (continued)

A similar question could be asked about baseline CRP. Paul Ridker has argued eloquently that CRP and IL-6 are primary drivers of cardiovascular risk and that statins alone do not provide sufficient protection in this regard.

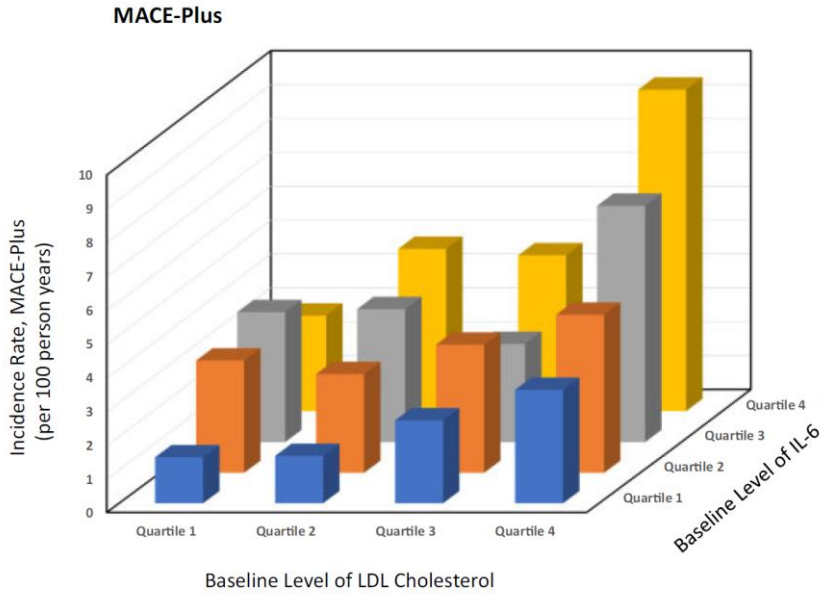
Ridker et.al. (2020)*: "IL-6, the primary cytokine driving hepatic CRP production, sits at a crucial juncture in a proven pathway linking inflammation to vascular events. Mendelian randomization studies have found polymorphism in the IL-6 signalling pathway to associate with lifelong hsCRP levels and lifelong vascular risk. The large-scale CANTOS inflammation inhibition trial has shown that the magnitude of anti-cytokine benefit in atherothrombosis relates directly to the magnitude of inflammation reduction achieved.

Very recently, the COLCOT trial has shown that anti-inflammatory therapy with colchicine can also reduce vascular events, a finding of interest as this microtubule inhibitor may also have impact on the NLRP3 inflammasome and hence downstream production of both IL-6 and hsCRP."

Novo Nordisk is in the middle of a large Phase 3 trial called ZEUS of an anti IL-6 therapy in persons with high cardiovascular risk.

An obvious question is whether obesity is a third risk factor that should be in a chart like at right. Does an anti-IL6 drug obviate the need for a GLP-1? We would think, probably not? Or, conversely, is there still a need for an IL-6 drug after patients get a GLP-1? We would also think also unlikely. One could imagine a world where patients get a triple therapy (PCSK9 or statin) + (IL-6 or NLRP3) + obesity drug (GLP-1 agonist + whether the future will bring). Obviously, new lipid interventions in development by companies like Verve/Lilly, New Amsterdam Therapeutics and the like could become very important in this context.

CIRT Study: Cholesterol and Inflammation Drive CV Events



* See Ridker PM, MacFadyen JG, Glynn RJ, Bradwin G, Hasan AA, Rifai N. Comparison of interleukin-6, C-reactive protein, and low-density lipoprotein cholesterol as biomarkers of residual risk in contemporary practice: secondary analyses from the Cardiovascular Inflammation Reduction Trial. Eur Heart J. 2020;41(31):2952-2961. (Link)

Rationale for Payor Coverage of Semaglutide Reasonably Good Based on SELECT Data

The AE table showed that the incidence of adverse events is about 3% lower on obese persons with Semaglutide. That's over 3 years.

These are not garden-variety adverse events: central nervous disorders, infections, respiratory disorders. These types of events can involve hospitalizations and long-term chronic care.

The average cost in Medicare, for example, of a COPD patient is around $21,000.* In contrast, a healthy person in Medicare costs less than $5,000. The incremental cost is $16,000. But that's for *one disease* for *one year*.

From a lifetime/NPV perspective, one could reasonably assume that the cost savings from avoiding cases of chronic disease with Semaglutide works out to $75,000 per person who gets an "adverse event". Who knows, maybe it's more. It's hard to tell exactly from the NEJM table.

So, with a 1% reduction in events that cost $75,000 each per year, one would be willing to spend $750 on drugs to break even from a cost saving perspective. This compares to current annual cost of Semaglutide to an insurer of roughly $3,500. Thus, there is no evidence that insurers would experience a net cost reduction from covering Semaglutide.

However, this analysis only looks purely at whether an insurer could reduce spend by covering semaglutide in the types of persons who were in the SELECT study. ICER likes to look QALY's (years of life gained) and assigns a significant positive value to these. In this sense, it appears quite likely that it could easily pay off. Indeed, ICER analysis is reasonably positive on Semaglutide.** The new body of evidence in Saturday's NEJM article shows a much broader case for covering semaglutide than that considered by ICER in 2002.

* Source: https://www.hmpgloballearningnetwork.com/site/jcp/article/health-care-use-and-costs-among-medicare-patients-chronic-obstructive-pulmonary-disease

** Source: https://www.washingtonpost.com/opinions/2023/10/31/obesity-drugs-ozempic-wegovy-semaglutide-costs/

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

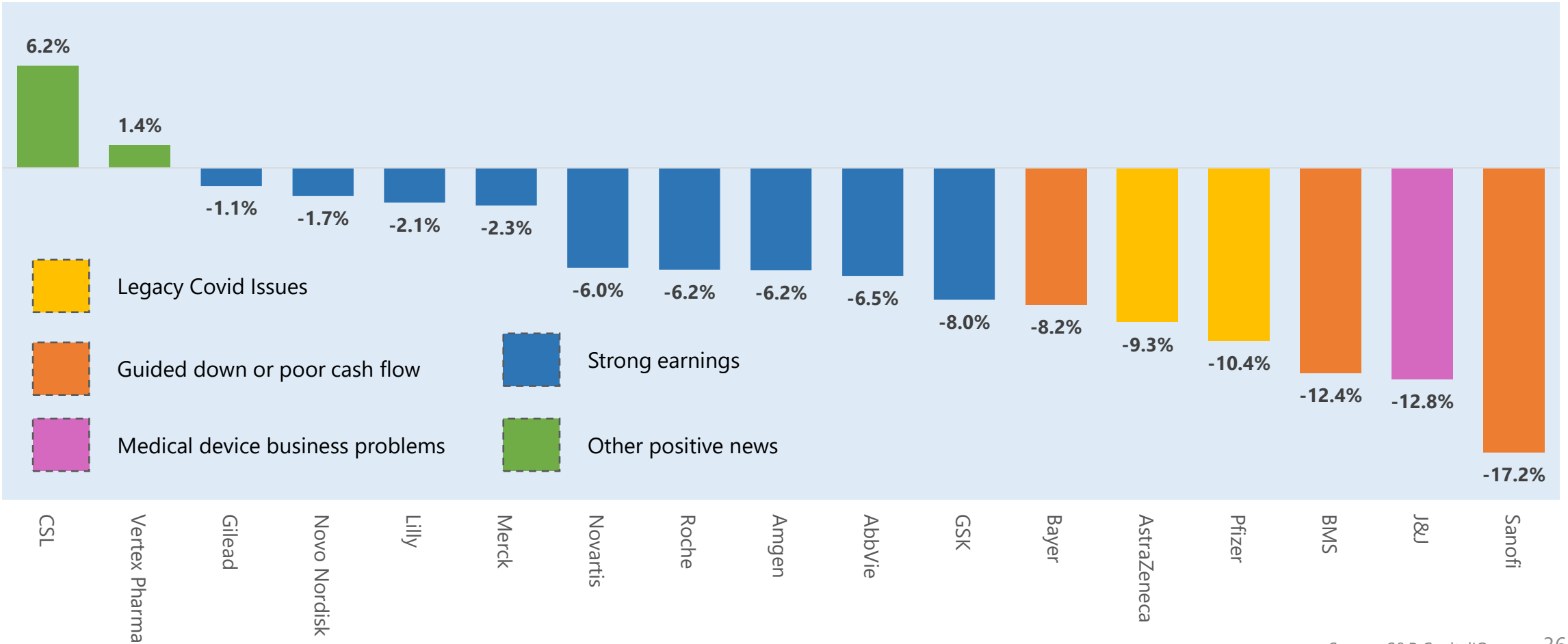
Big Pharma Earnings Update

Roche Headquarters Complex, Basel Switzerland

Assessing Pharma Earnings Season

It's been a tough Q3 earnings season for pharma. The median share price return has been negative 6.2% despite the fact that most companies met or beat expectations for earnings. Only a few players had bad news on earnings, guidance or results (Bayer, BMS, Sanofi). On the whole, the market is reducing exposure to pharma on worries – perhaps due to difficulties in launching products. This is evident in the drops in value over the last month in companies that were able to report strong earnings.

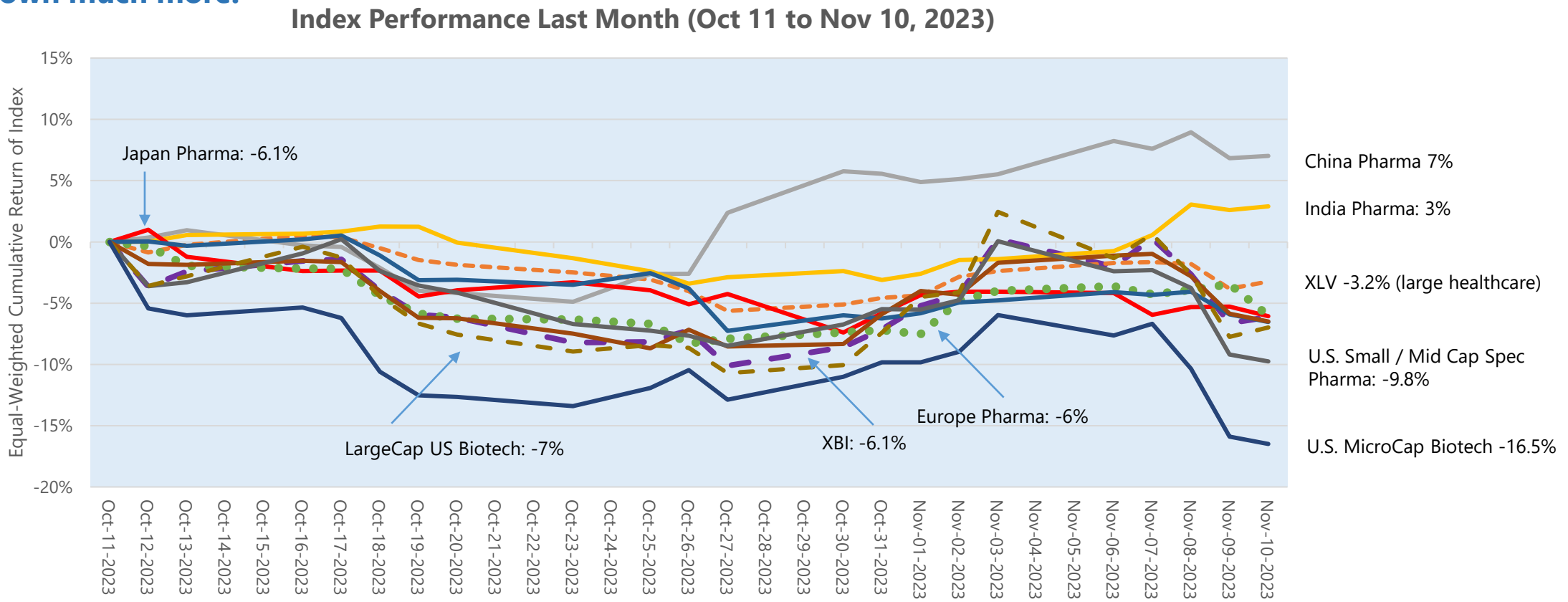
Share Price Return, October 11 to November 10, 2023



Source: S&P CapitalIQ.

Big Pharma Performance Last Month In Line with Other Biopharma Subectors

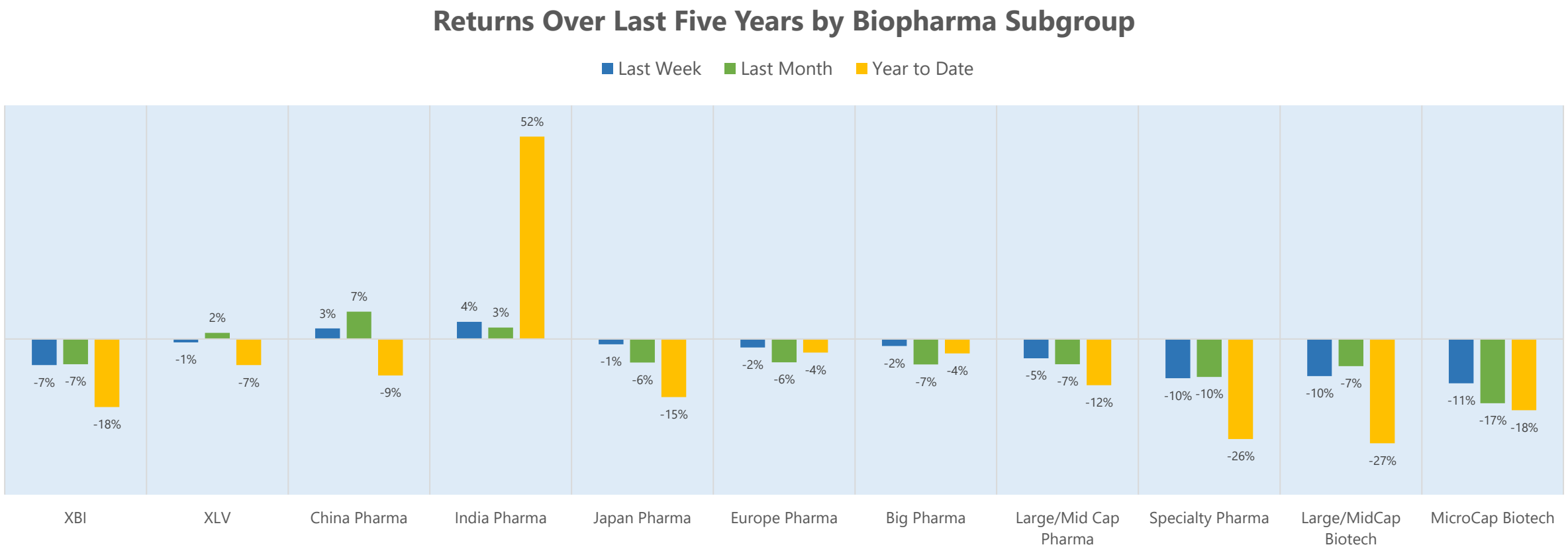
The only segments that have traded up in the last month are China (up 7%) and India (up 3%). The XBI, Japan Pharma, Big Pharma, Europe Pharma and U.S. large cap biotech are all down 6 to 7 percent. Microcap biotech is down much more.



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

Specialty Pharma and Biotech Doing Poorly This Year. India Pharma Doing the Best.

Performance this year strongest in India and weakest in large/midcap biotech and specialty pharma. Big pharma are down 4% for year. Not bad compared to XBI, XLV, China and large/midcap pharma.



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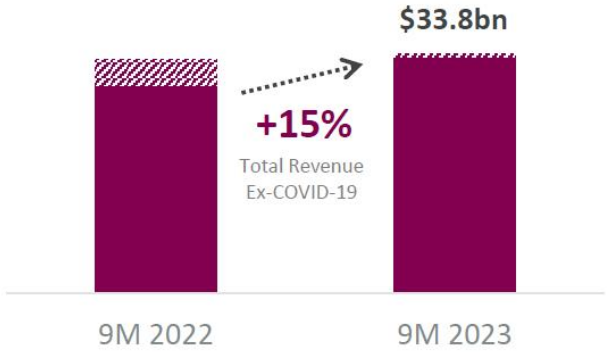
Benefitting from broad-based, diverse sources of revenue

Strong commercial performance and financial delivery in 9M 2023

Total Revenue | +5%

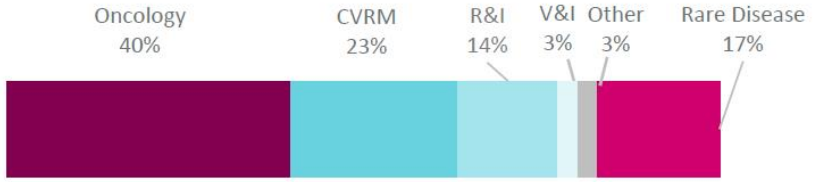


Core EPS | +17%

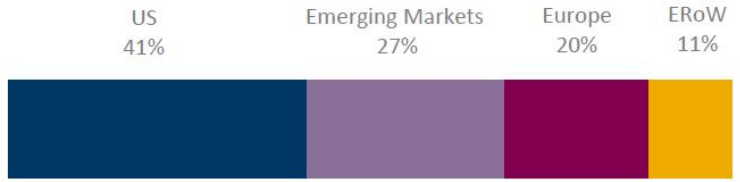
Vaxzevria/COVID-19 mAbs[1]
Total Revenue

Broad-based, diverse source of Total Revenue

9M 2023 | % Total Revenue by therapy area



9M 2023 | % Total Revenue by geography

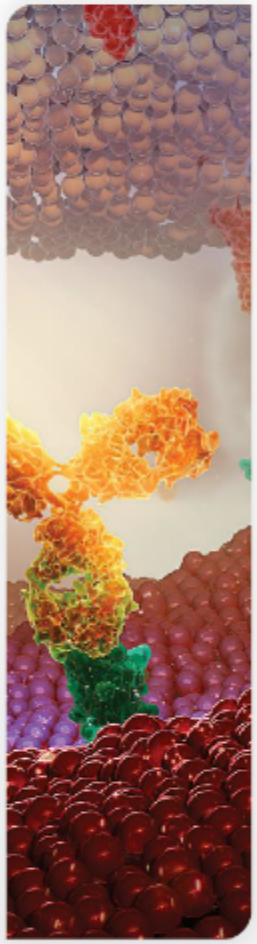


2023 guidance updated: Core EPS now expected to increase by a low double-digit to low-teens %

All growth rates at CER. Due to rounding, the sum of a number of dollar values and percentages may not agree to totals.
1. COVID-19 mAbs = *Evusheld* and AZD3152, the antibody currently in development. CER = constant exchange rates; mAb = monoclonal antibody; EPS = earnings per share; CVRM = Cardiovascular, Renal & Metabolism; R&I = Respiratory & Immunology; V&I = Vaccines & Immune Therapies; ERoW = Established Rest of World.

Oncology – R&D highlights

Establishing AstraZeneca portfolio of differentiated ADCs



Five wholly owned ADCs already in the clinic

Clinical stage trials ongoing in lung, breast, haematology, GYN/GU and GI

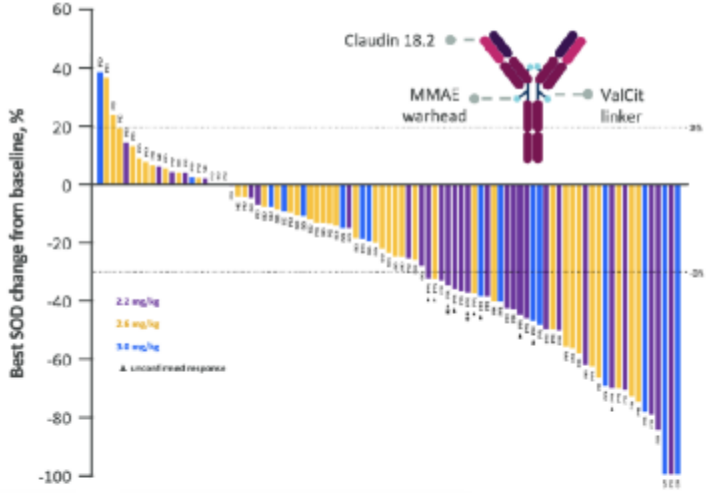
	PRECLINICAL	PHASE I	PHASE II	PHASE III	INDICATIONS OF INTEREST
AZD8205 (B7H4) DAR 8					Breast, BTC, ovarian, endometrial
AZD9592 (EGFR/cMET) DAR 6					NSCLC, HNSCC
AZD5335 (FRα) DAR 8					Ovarian, lung
AZD0901 (CLDN18.2) DAR 4					Gastric, GEJ, pancreatic
LM-305 (GPRC5D) DAR 4					Multiple myeloma

AZD0901

Promising efficacy in gastric / GEJ cancer

BoR in gastric / GEJ cancer (IHC 2+, ≥20% TC)[1]

Phase I dose escalation / expansion



Broader clinical development programme in progress

1. Xu RH et al. Abstract 434420 presented at ASCO Virtual Plenary on 7 November 2023. ADC images for illustrative purposes only; actual drug positions may vary.

ADC = antibody drug conjugate; GYN = gynaecological; GU = genitourinary; GI = gastrointestinal; B7H4 = B7 homolog 4; DAR = drug to antibody ratio; EGFR= epidermal growth factor receptor; cMET =mesenchymal-epithelial transition factor ; FRα = folate receptor alpha; CLDN18.2 – claudin 18.2; CPRC5D – G-protein coupled receptor C family 5D; TOP1i – topoisomerase 1 inhibitor; MMAE – monomethyl auristatin E; BTC – biliary tract cancer; NSCLC – non-small cell lung cancer; HSNCC – head and neck squamous cell carcinoma; GEJ – gastroesophageal junction; BoR – best overall response; IHC – immunohistochemistry; TC – tumour cell; CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; NE – not evaluable.

Collaboration partner: Keymed Biosciences (AZD0901).

BioPharmaceuticals

Accelerating presence in obesity with ECC5004, a novel once-daily oral GLP-1RA

ECCOGENE 诚益生物

ECC5004 (GLP-1RA)

global development
and commercialisation rights[1]

Potential for no titration

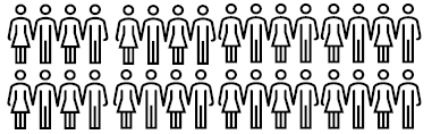
High bioavailability, favourable tolerability profile

Novel once-daily oral small molecule

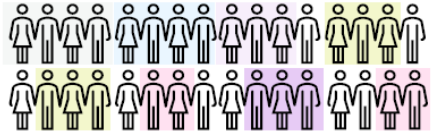
Efficacy at low doses – 10 to 30mg

Phase II planned 2024

Significant market opportunity in obesity



1bn people living with obesity



Obesity is driver for **>200 chronic diseases**

Diabetes, dyslipidemia, hypertension, HF, renal disease, NASH

Opportunity beyond obesity to address cardiometabolic disease

Farxiga	AZD6234 LA Amylin	baxdrostat ASI	mitiperstat MPO	AZD5462 oRXFP1	AZD0780 oPCSK9
on-market	Phase I	Phase III	Phase II	Phase I	Phase I

Strong track record in cardio renal metabolic diseases, opportunity for monotherapy and combinations to address broad range of co-morbid diseases

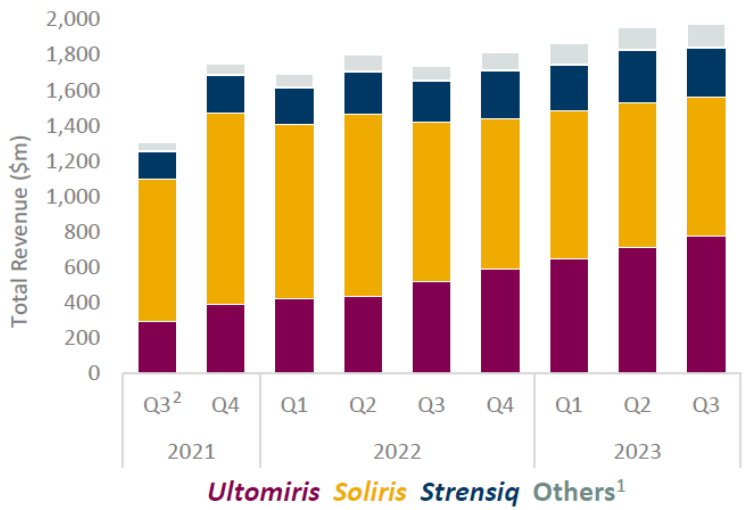
1. In China, Eccogene and AstraZeneca will operate under co-development and co-commercialisation agreement. GLP-1RA = glucagon-like peptide 1 receptor agonist; HF = heart failure; NASH = non-alcoholic steatohepatitis; LA = long-acting; ASI = aldosterone synthase inhibitor; MPO = myeloperoxidase; oRXFP1 = oral relaxin family peptide receptor 1; oPCSK9 – oral proprotein convertase subtilisin/kexin type-9.

Rare Disease – 9M and Q3 2023

Strong double-digit growth in 9M 2023 with Total Revenue +12%, momentum into year-end

Total Revenue by medicine

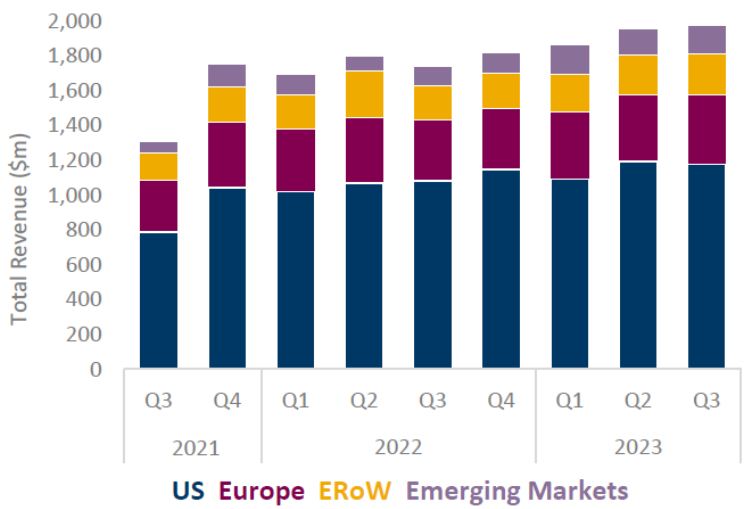
9M 2023 $5.8bn, +12%



Q3 dynamics

- ***Ultomiris*** +49%, neurology demand, new market access; ***Soliris*** (12%), successful conversion
- ***Strensiq*** +21%, and ***Koselugo*** +81%, new patient demand

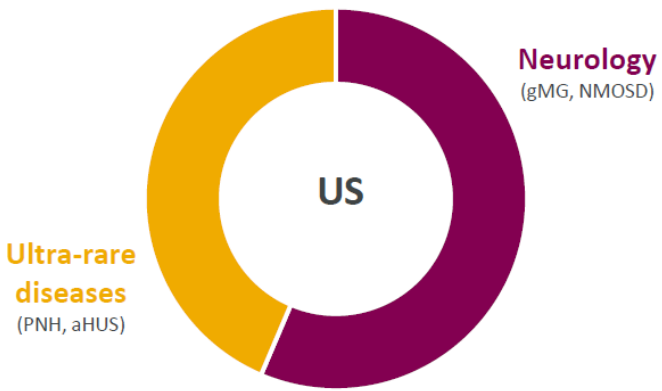
Total Revenue by region



Q3 dynamics

- **US** +9% and **EU** +8%, neurology demand
- **ERoW** +22%, neurology demand, expanded access
- **Emerging Markets** +70%, demand growth, expanded access

C5 franchise indications



Key dynamics

- Neurology growing proportion of C5 franchise
- Smaller proportion from ultra rare disease, PNH and aHUS

All growth rates at CER.
1. Includes *Kanuma* and *Koselugo*. 2. Q3 2021 Total Revenue reported only comprise of those booked by AstraZeneca following completion of the acquisition of Alexion on 21 July 2021.
EU = Europe; ERoW = Established Rest of World; C5 = C5 inhibitors *Ultomiris* and *Soliris*; NMOSD = neuromyelitis optica spectrum disorder; gMG = generalised myasthenia gravis; PNH = paroxysmal nocturnal hemoglobinuria; aHUS = atypical hemolytic uremic syndrome; CER = constant exchange rates.
Collaboration partners: Merck & Co., Inc. (*Koselugo*).

Gilead Q323 Key Takeaways

GILEAD
Advancing Therapeutics.
Improving Lives.

Financial Results

- Q323 Total Product Sales excl. Veklury +5% YoY to $6.36B
- Total HIV +4% YoY due to higher demand & inventory, offset by price; Biktarvy +12% YoY to $3.09B
- Oncology +33% YoY to $769M driven by ongoing demand across Trodelvy and Cell Therapy
- YTD Total Product Sales excl. Veklury +10% YoY; Oncology +42% and Virology +7%

Virology Updates

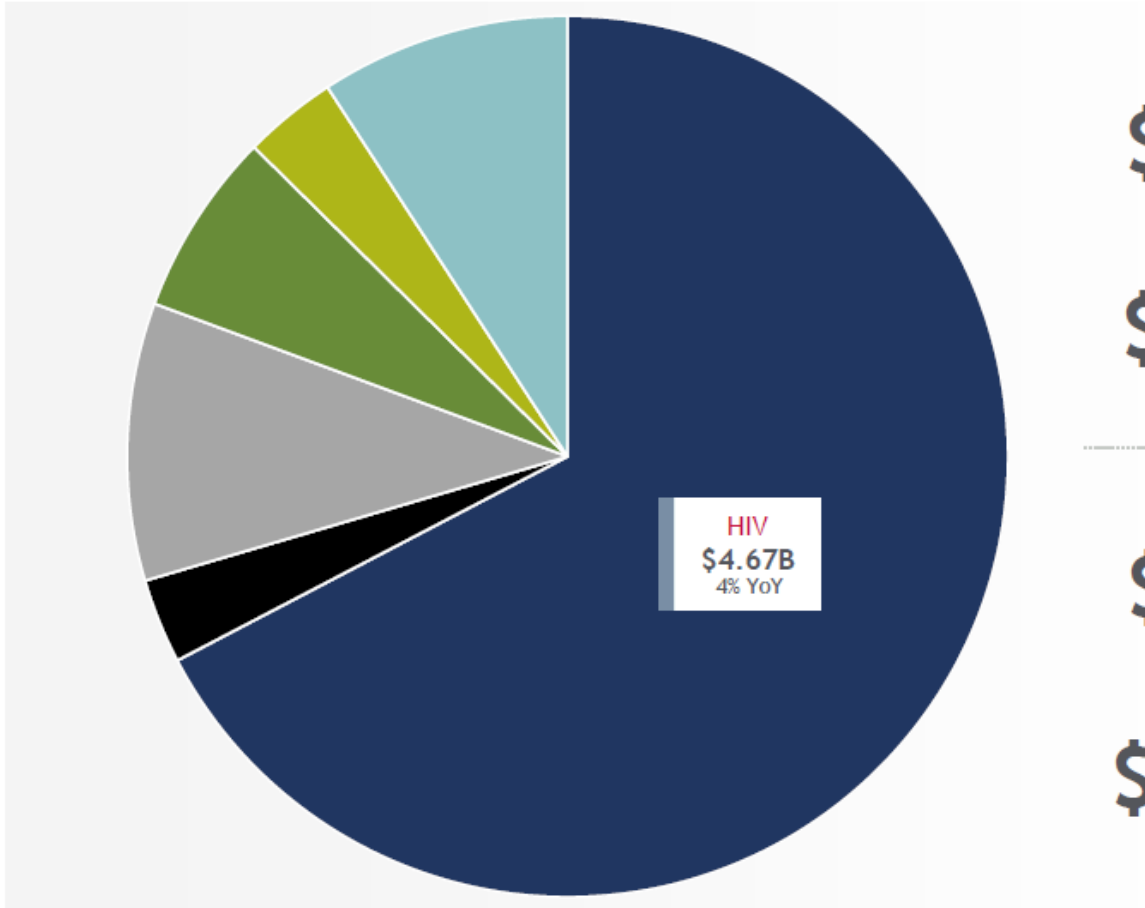
- Phase 1 GS-1720 & Phase 2 ARTISTRY-1 BIC/LEN data promising; presentation at a 2024 conference
- Phase 3 PURPOSE-1 trial of lenacapavir for HIV prevention completed enrollment
- Phase 3 OAKTREE trial of obeldesivir in standard-risk COVID-19 patients completed enrollment
- FDA & EC approval to extend use of Veklury to treat COVID-19 in patients with hepatic impairment

Oncology Updates

- Trodelvy received EC approval for pre-treated HR+/HER2- mBC
- EVOKE-02 supports PoC for Trodelvy plus pembrolizumab in 1L PD-L1 High mNSCLC at WCLC 2023
- Encouraging Trodelvy data from TROPiCS-03 SCLC and HNSCC cohorts presented at ESMO 2023
- EDGE-Gastric data reinforces potential of dom + zim + chemo for 1L upper GI cancers at ASCO Plenary

EC - European Commission, ESMO - European Society of Medical Oncology, HNSCC - Head and neck squamous cell carcinoma, NSCLC - Non-small cell lung cancer, PoC - Proof-of-concept, SCLC - Small cell lung cancer, UC - Ulcerative colitis

Solid Q323 Base Business Performance



$7.0B **Total Product Sales**
Flat YoY, 7% QoQ

$6.4B **Total Product Sales excluding Veklury**
5% YoY, 1% QoQ

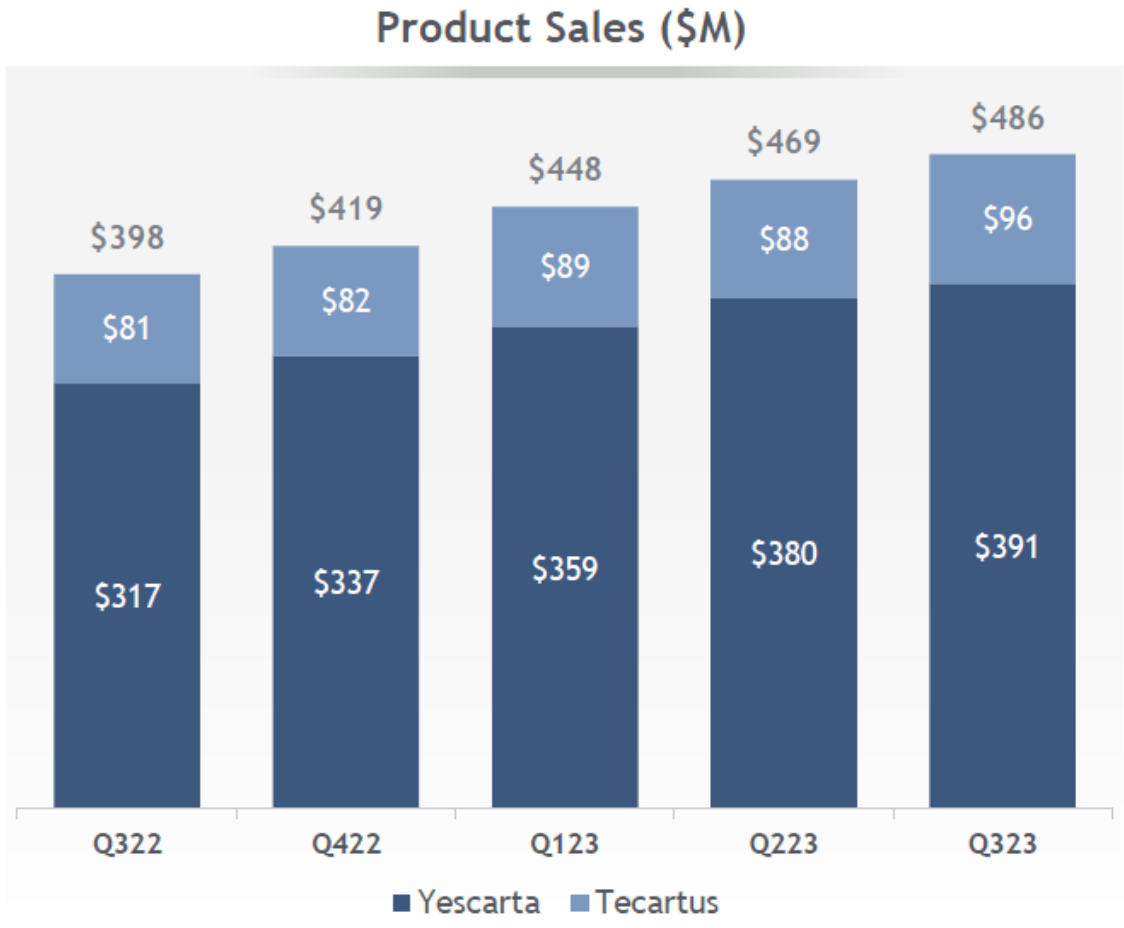
$4.7B **HIV Product Sales**
4% YoY, 1% QoQ

$769M **Oncology Product Sales**
33% YoY, 6% QoQ

(in $M except as otherwise noted)

Note: Liver Disease includes: chronic hepatitis B virus, chronic hepatitis C virus and chronic hepatitis delta virus. YoY reflects Q323 vs Q322 and QoQ reflects Q323 vs Q223.

Cell Therapy: Expanding Demand Globally



YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

Q323 sales +23% YoY; +3% QoQ

- YoY growth driven by strong underlying demand in R/R large B-cell lymphoma outside of the U.S.

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

Q323 sales +18% YoY; +8% QoQ

- YoY growth driven by increased demand for R/R mantle cell lymphoma and adult acute lymphoblastic leukemia

15 R/R - relapsed or refractory. Note: YoY reflects Q323 vs Q322 and QoQ reflects Q323 vs Q223.

Gilead Execs Muse Over ‘Surprising’ Lack of CAR-T Adoption in Certain Patients, US Barriers to Uptake

Zoey Becker, *FiercePharma*, Nov 8, 2023 (excerpt)

With the goal of becoming a powerhouse in oncology, Gilead Sciences is closely tracking the progress of its two marketed CAR-T therapies.

Armed with its CAR-T unit Kite Pharma and FDA-approved therapies Yescarta and Tecartus, the company has a pulse on the hot market and has identified some factors hampering cell therapy growth in the U.S.

This past quarter, Kite’s cell therapies Yescarta and Tecartus delivered sales gains of 23% and 18%, respectively. Tecartus pulled down $96 million, while Yescarta generated $391 million but missed analyst estimates of $417 million, according to Third Bridge analyst Lee Brown.

On Gilead's quarterly conference call Tuesday, Chief Commercial Officer Johanna Mercier said it was “surprising” that only about 10% of eligible second-line large B-cell lymphoma patients are undergoing cell therapy treatment “given the strong clinical data."

Describing the situation, Kite’s new head Cindy Perettie attributed the gradual uptake to “specific barriers” that mainly exist in the U.S. market.

While uptake has been faster in Europe due to “socialized medicine” systems that allow patients quicker access after reimbursement talks, the U.S. is hampered by “the fragmentation of the healthcare system,” Perettie said.

Around 80% of oncology patients are treated in their local communities, Perettie explained, but most of the company's authorized treatment centers "exist in large academic hospitals."

Source: https://www.fiercepharma.com/pharma/gilead-muses-over-surprising-lack-car-t-adaption-us-specific-barriers

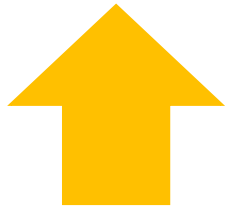
Third Quarter Below Prior Year as Expected – Group Outlook Confirmed

Nov 8, 2023

1. Group sales of 10.342 billion euros (Fx & portfolio adj. minus 0.2 percent)
2. EBITDA before special items: 1.685 billion euros (minus 31.3 percent)
3. Sales stable at Crop Science and Pharmaceuticals and up slightly at Consumer Health (Fx & portfolio adj.)
4. Earnings lower at all divisions, especially Crop Science
5. Core earnings per share at 0.38 euros (minus 66.4 percent)
6. Net income at minus 4.569 billion euros, impacted by impairment losses at Crop Science due to interest rates
7. Free cash flow at 1.626 billion euros
8. CEO Anderson: "We are redesigning Bayer to focus only on what's essential for our mission, 'Health for all, hunger for none'"
9. Structural options remain under review

Full Year Outlook Confirmed

in €	FY 2023e at constant currencies [1]	Estimated FX Impact [2]
Net Sales	48.5bn – 49.5bn	-1.7bn
EBITDA (before special items)	11.3bn – 11.8bn	-0.2bn
Core EPS	6.20 – 6.40	not material
Free Cash Flow	~ 0bn	
Net Financial Debt	~ 36bn	



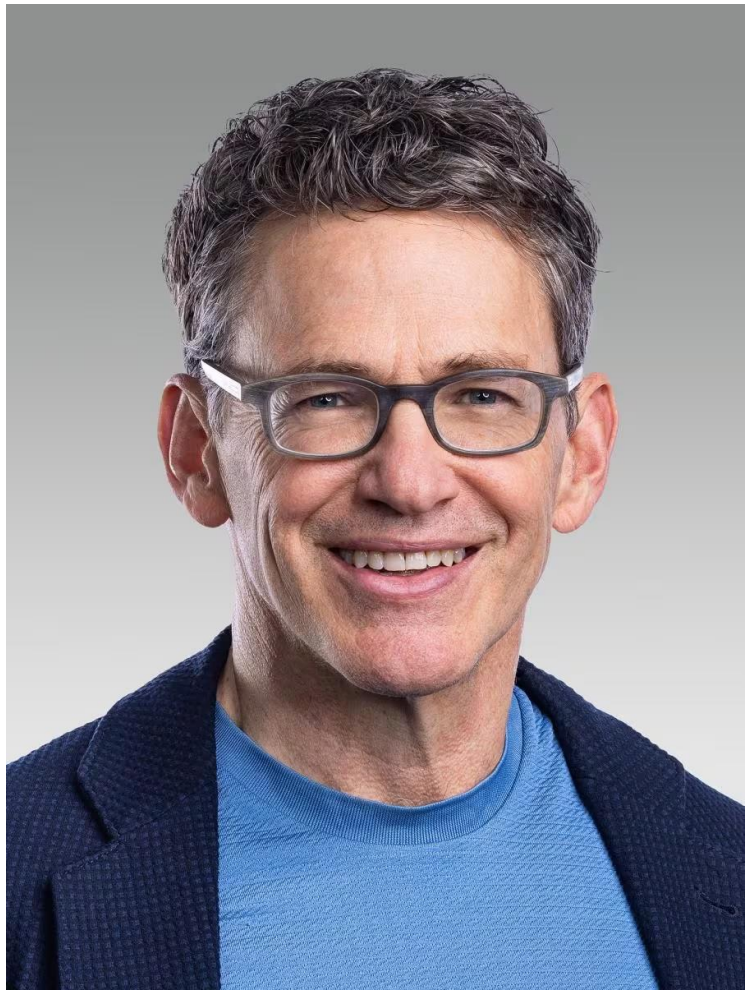
Odd to see a mature company with $50bn+ in revenue and zero free cash flow.

Source: https://www.bayer.com/media/en-us/third-quarter-below-prior-year-as-expected---group-outlook-confirmed/

Bayer to Focus on Health and Hunger Mission

Bayer Quarterly Earnings Press Release, November 7, 2023

"We're not happy with this year's performance. **Nearly 50 billion euros in revenue but zero cash flow is simply not acceptable,"** stated Anderson, who has been at the helm of the company since June. He intends to focus everything on Bayer's mission of "Health for all, hunger for none," and on driving innovation and strengthening financial performance. "Our mission hasn't always been front and center in our operations. That will change. We are redesigning Bayer to focus only on what's essential for our mission – and getting rid of everything else." By the end of next year, Bayer will remove multiple layers of management and coordination, he said. "This step will unleash our teams with the mission-focus necessary to turn things around. 95 percent of the decision-making in the organization will shift from managers to the people doing the work." Even though this will include a significant reduction in the workforce, it is not a traditional cost-cutting program, Anderson said. In addition, a new Board of Management compensation system will be proposed at the next Annual Stockholders' Meeting, he said, noting that it will be more closely aligned with the long-term development of the company's share price.



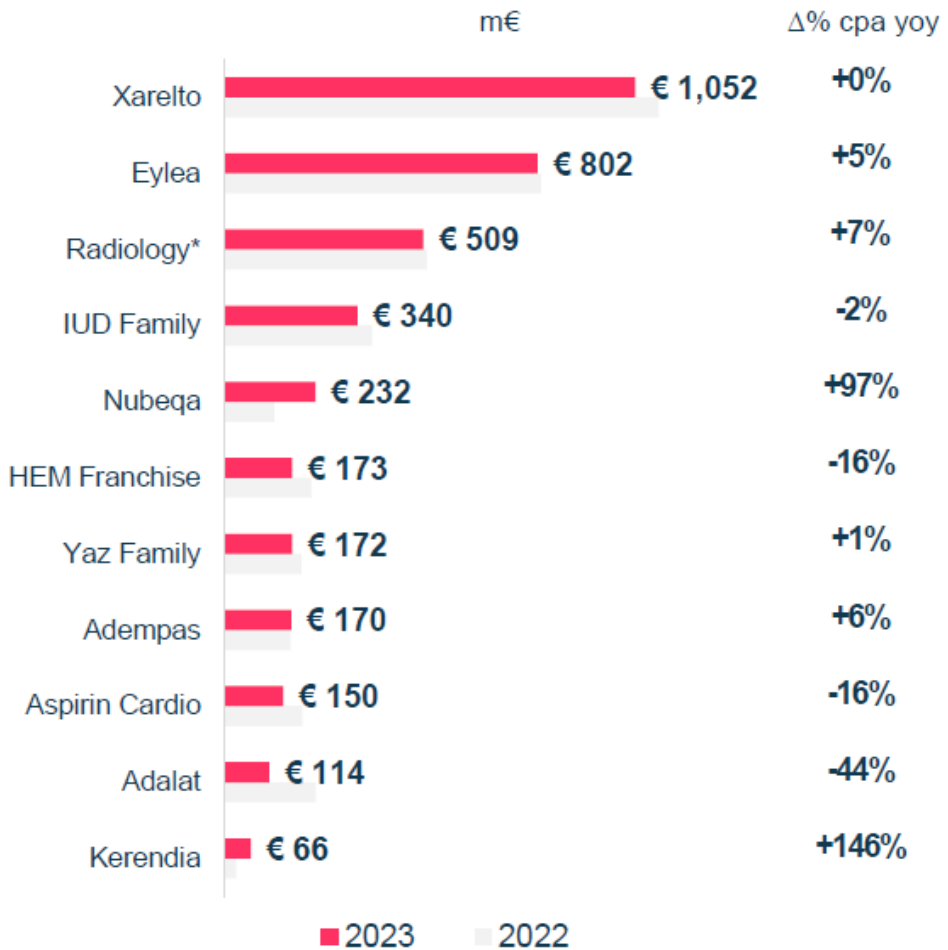
Bill Anderson, CEO, Bayer

Source: https://www.bayer.com/media/en-us/third-quarter-below-prior-year-as-expected---group-outlook-confirmed/

Q3: Launch Assets, Eylea and Radiology Business With Ongoing Strong Performance, Offsetting Softness in Mature Portfolio

Pharmaceuticals
Q3 2023

Q3 2023 Sales by Key Products



* Radiology comprises 13 brands in total, among others CT Fluid Delivery, Ultravist and Gadovist product family

Key Drivers

- **Xarelto:** solid volume growth in major markets offset by UK pricing and China headwinds and lower US royalties
- **Eylea:** continued strong volume trend in all marketed regions partially held back by softer pricing, particularly in Europe
- **Nubeqa:** sales almost doubled again, being the fastest growing ARI[1] in the US
- **Kerendia:** growth driven by continued US market uptake
- **Radiology:** substantial sales gain, particularly for CT Fluid Delivery and Ultravist
- **IUD Family:** volume declines largely compensated by higher prices
- **HEM Franchise:** decline mostly due to competition, mainly in US and China
- **Aspirin Cardio:** sales decline driven by lower channel demand
- **Adalat:** sales continued to be impacted by VBP in China

[1] ARI: Androgen Receptor Inhibitor

Considering Separating Consumer Health or Crop Science

Bayer Quarterly Earnings Press Release, November 7, 2023

"We are looking closely at our structural options. We have an expert team – including external financial advisors – evaluating them. They're reviewing market conditions, what structural changes would mean for our value creation, one-time costs and dis-synergies, cash flows and leverage ratios, tax leakage, and other criteria," Anderson explained. **In terms of structural options, beyond maintaining three divisions, a separation of either Consumer Health or Crop Science remains under evaluation.** "We have also taken some options out of consideration. For example, we considered simultaneously splitting the company into three businesses. We're ruling that option out. A three-way split would require a two-step process." The company will share further details in March at its Capital Markets Day together with the publication of the Annual Report and the 2024 guidance. Based on current market dynamics and first assumptions, Bayer expects a soft growth outlook and continued challenges to the company's profitability for next year.

Source: https://www.bayer.com/media/en-us/third-quarter-below-prior-year-as-expected---group-outlook-confirmed/

Executing on potential top and bottom-line growth drivers

3 recent FDA approvals and ongoing/upcoming launches

LEQEMBI is the first anti-amyloid antibody to receive traditional approval for Early AD

ZURZUVAE is the first oral therapy specifically approved for adults with PPD in the U.S.

QALSODY is the first treatment to target a genetic cause of ALS

Acquisition of Reata Pharmaceuticals adds fourth launch opportunity

Acquisition adds a highly complementary and profitable product in ***SKYCLARYS***, the only approved therapy for Friedreich's ataxia

Leveraging Biogen rare disease capabilities to expand access globally

Expected to meaningfully contribute to Biogen's operating profit beginning in 2024

Reengineering the company with Fit For Growth program

Refocusing resources to support in-market growth opportunities, new product launches and R&D in areas of expected future growth

Simplifying the organizational structure to increase agility and accountability

Initiative is expected to result in meaningful cost savings to support sustainable growth

Note: LEQEMBI (lecanemab-irmb) is being developed in collaboration with Eisai Co., Ltd; Eisai serves as the lead for lecanemab development and regulatory submissions globally; See LEQEMBI USPI for full prescribing information; ZURZUVAE is being developed in collaboration with Sage Therapeutics, Inc.; See ZURZUVAE USPI for full prescribing information; QALSODY is licensed from Ionis Pharmaceuticals, Inc; See QALSODY USPI for full prescribing information; See SKYCLARYS USPI for full prescribing information
AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; PPD = postpartum depression

Updating full year 2023 financial guidance

	Prior FY 2023 Guidance	Updated FY 2023 Guidance
Revenue	**Mid-single digit percentage decline***	**Low-single digit percentage decline***
Non-GAAP Diluted EPS	**$15.00 to $16.00**	**$14.50 to $15.00** Reflecting ~$0.75 of dilution from Reata acquisition, which closed September 26, 2023

* Versus reported revenue for full year 2022

Please see Biogen's third quarter 2023 earnings release, available at the Investors section of Biogen's website at investors.biogen.com, for additional 2023 financial guidance assumptions.

Biogen may incur charges, realize gains or losses, or experience other events or circumstances in 2023 that could cause any of these assumptions to change and/or actual results to vary from this financial guidance.

Please see slide 2 of this presentation for additional information on our use of Non-GAAP measures, including forward-looking Non-GAAP financial measures.

Leqembi Launch Has Been Soft

Biogen says growth is coming, but won't specify when

CEO Chris Viehbacher said the company has "the elements to think about a return to topline growth." Yet, that goal hinges on the successful launch of multiple new products.

Jacob Bell, *Biopharma Dive*, Nov 8, 2023

"This was always going to be a gradual launch," Viehbacher said. "Obviously, sales will be expected to ramp at some point. But it has always been a difficult product to forecast because there's just no real good analogs here."

The FDA granted conditional approval to an intravenous version of Leqembi in January, followed by a first-of-its-kind full clearance in July. But challenges from insurers and the broader healthcare system have hindered the drug's sales, which, according to Eisai, reached $2.7 million across the second and third quarters. Highlighting this, Viehbacher noted how the Cleveland Clinic, "one of the most respected medical centers in the world," just administered its first infusion of Leqembi early this month.

"I think we're seeing all of the green shoots of growth," he said. "But it is complex, and we're seeing varied response in terms of even medical centers."

Chris Viehbacher, CEO, Biogen

Source: https://www.biopharmadive.com/news/biogen-growth-third-quarter-earnings-alzheimers-postpartum-rare-disease/699157/

Immunology on the Brain

Jane Grogan, Biogen's new head of research, talks about immunology, rare diseases and her longstanding interest in the cancer target TIGIT.

Asher Mullard Interview with Jane Grogan, *Nature Reviews Drug Discovery*, Nov 8, 2023

Can you expand on your research priorities?

I am only a month in, so I'm still really looking at our portfolio. Clearly we've made some game-changing paradigm shifts in Alzheimer disease and so we will be maintaining a strong effort in building out delivery, diagnosis and what's next in that space. We'll continue to put our arms around rare diseases, and what that looks like in terms of modalities that we're currently working on. And then immunology will be something that we are in.

Across modalities?

One of the challenges for everyone is getting tissue-specific delivery of a drug into the tissue that you need. This is true in any disease area. How do you get specifically into a tumour when you're delivering a CAR T cell, for example? Can you do that with bispecifics? And how do you get drugs into hard-to-access compartments like the brain? I think we're seeing some really exciting advances in the field in terms of using receptors to shuttle drugs into the brain. That allows a few things, including direct access to your target. I think we're going to see a lot of growth in the next 5–10 years in this space. And I hope that understanding those pathways may inform how we think about specificity around gene therapy.

The CAR T pipeline has exploded in lupus, and there may be similar opportunities in multiple sclerosis. Is this something you are watching?

I think there's an opportunity there, and there are a few smaller companies out there trying to go after that. Just to put my company hat on, we remain really open to partnerships around modalities that are going to actually make an impact on patients. We're not about to start a cell therapy unit right now, but we're certainly staying abreast of the field.

How will you leverage your immunology expertise in the rare disease space?

The challenge and the thrill of working in the rare disease space is that you can truly contemplate cure. And being able to effect that with various different modalities is fantastic. One of the things that's left to explore is around the unmet medical need that is left when you think about cure, and whether there are side effects you might need to tackle from an immunological perspective.

Source: https://www.nature.com/articles/d41573-023-00183-w

Industry News

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

EU Proposal May Accelerate Pharma Innovation Decline, Industry Group Says

Julia Payne, *Reuters*, November 6, 2023

BRUSSELS, Nov 6 (Reuters) - A major pharmaceutical rules overhaul, proposed by the European Commission in April, could see Europe's share in global research and development contract by a third to 21% by 2040 translating to 2 billion euros ($2.15 billion) per year in lost investment, industry group EFPIA said on Monday.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) says the Commission has not conducted a competitiveness impact assessment and if the new rules become law, they would accelerate the negative innovation trend in the EU and hit small and medium-sized enterprises the hardest.

"Any changes to our incentives system would equally affect EU-based and foreign-based companies which bring medicines to the EU and, therefore, it would not put EU firms at a disadvantage," an EU Commission spokesperson said.

Medication was the single biggest contributor to the EU's trade surplus, with 235 billion euro ($252.13 billion) worth of exports in 2021.

The EFPIA said small biotech companies have already moved to the United States and China.

efpia
European Federation of Pharmaceutical Industries and Associations

Ongoing rule changes in Europe regarding exclusivity periods have potential to significantly reduce the attractiveness of the region for the pharma industry.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/eu-proposal-may-accelerate-pharma-innovation-decline-industry-group-says-2023-11-06/

Senate Confirms Monica Bertagnolli as NIH Director

Sen. Bernie Sanders held up the vote for months in a failed effort to push President Joe Biden to do more on drug pricing.

Kelly Hooper and Erin Schumaker, *Politico*, November 8, 2023

The Senate confirmed Dr. Monica Bertagnolli to lead the National Institutes of Health in a 62-36 vote Tuesday.

Nearly every Democrat joined 13 Republicans in filling the post responsible for overseeing billions in federal research grants, but vacant since Dr. Francis Collins left nearly two years ago.

"Dr. Bertagnolli is the right person to ensure the NIH stays on the cutting edge of innovation and research and fulfills its critical mission to promote health, improve equity, keep our nation competitive and give patients across the world real hope for the future," said Senate Appropriations Chair Patty Murray (D-Wash.) in a speech just before the vote.

While Bertagnolli won confirmation with ease, her road there was rocky. After President Joe Biden tapped her to lead NIH in May, Sen. Bernie Sanders (I-Vt.) held up her nomination for months in an effort to extract a comprehensive plan to lower drug prices from the White House.

He and Pennsylvania Sen. John Fetterman were the only members of the Democratic caucus to vote against confirmation. Thirty-four Republicans also voted no.

Source: https://www.politico.com/news/2023/11/07/senate-nih-director-monica-bertagnolli-00125803

FDA Approves Lilly's Zepbound™ (tirzepatide) for Chronic Weight Management

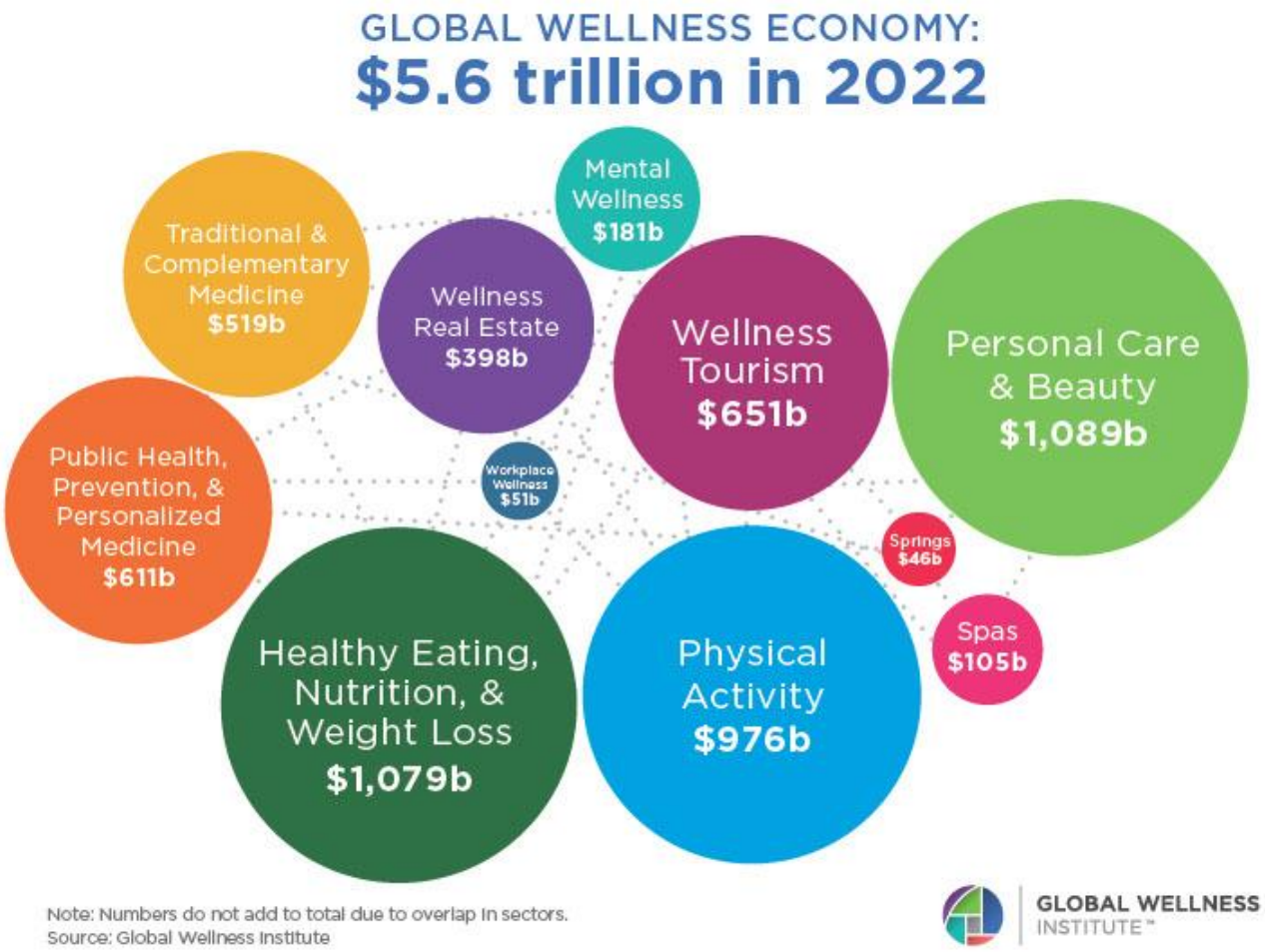
INDIANAPOLIS, Nov. 8, 2023 /PRNewswire/ -- The U.S. Food and Drug Administration (FDA) approved Eli Lilly and Company's (NYSE: LLY) Zepbound™ (tirzepatide) injection, the first and only obesity treatment of its kind that activates both GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) hormone receptors. Zepbound is indicated for adults with obesity (with a BMI of 30 kg/m2 or greater), or those who are overweight (with a BMI of 27 kg/m2 or greater) and also have weight-related medical problems such as hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease, to lose weight and keep it off. It should be used with a reduced-calorie diet and increased physical activity. Zepbound should not be used with other tirzepatide-containing products or any GLP-1 receptor agonist medicines, and it has not been studied in patients with a history of pancreatitis, or with severe gastrointestinal disease, including severe gastroparesis.

"Obesity is a chronic disease that can result in serious health complications, including heart disease, stroke and diabetes. Despite our knowledge of obesity as a treatable, chronic disease, people living with obesity still face many challenges in their health and weight management journey," said Joe Nadglowski, president and chief executive officer of the Obesity Action Coalition. "New treatment options bring hope to the many people with obesity who struggle with this disease and are seeking better options for weight management."

The approval was based on results from the phase 3 SURMOUNT-1 and SURMOUNT-2 trials. In SURMOUNT-1, a study in 2,539 adults with obesity, or excess weight and weight-related medical problems not including diabetes, people taking Zepbound as an adjunct to diet and exercise experienced substantial weight loss compared with placebo at 72 weeks. At the highest dose (15 mg), people taking Zepbound lost on average 48 lb., while at the lowest dose (5 mg), people lost on average 34 lb. (compared to 7 lb. on placebo).

Source: https://investor.lilly.com/news-releases/news-release-details/fda-approves-lillys-zepboundtm-tirzepatide-chronic-weight

Global Wellness Economy Gigantic



Wellness Economy Growth Projections 2022-2027

	Market Size (US$ billions)		Projected Market Size (US$ billions)					Projected Average Annual Growth Rate
	2019	2022	2023	2024	2025	2026	2027	2022-2027
Healthy Eating, Nutrition, & Weight Loss	**$911.3**	**$1,079.3**	$1,161.7	$1,240.4	$1,325.6	$1,411.0	$1,500.7	*6.8%*
Personal Care & Beauty	**$1,066.3**	**$1,088.7**	$1,183.2	$1,246.5	$1,310.7	$1,373.0	$1,437.7	*5.7%*
Wellness Tourism	**$720.4**	**$650.7**	$867.9	$1,029.5	$1,152.6	$1,275.1	$1,399.6	*16.6%*
Physical Activity	**$875.9**	**$976.3**	$1,058.5	$1,126.3	$1,202.3	$1,275.7	$1,352.4	*6.7%*
Wellness Real Estate	**$225.2**	**$397.7**	$472.7	$566.6	$667.0	$770.1	$887.5	*17.4%*
Traditional & Complementary Medicine	**$486.6**	**$518.6**	$569.5	$615.1	$662.1	$713.1	$768.2	*8.2%*
Public Health, Prevention, & Personalized Medicine	**$358.2**	**$610.9**	$613.1	$625.6	$637.9	$646.2	$661.4	*1.6%*
Mental Wellness	**$130.2**	**$180.5**	$201.8	$229.6	$258.8	$292.0	$330.2	*12.8%*
Spas	**$113.8**	**$104.5**	$122.0	$133.3	$141.3	$148.8	$156.1	*8.3%*
Thermal/Mineral Springs	**$65.7**	**$46.3**	$57.9	$66.6	$74.5	$82.4	$90.5	*14.3%*
Workplace Wellness	**$52.2**	**$50.6**	$52.0	$53.3	$54.8	$56.5	$58.4	*2.9%*
Wellness Economy	**$4,931.7**	**$5,611.6**	**$6,262.6**	**$6,818.1**	**$7,356.3**	**$7,893.9**	**$8,470.6**	*8.6%*

Note: Figures do not sum to total due to overlap in segments.
Source: Global Wellness Institute estimates, based upon economic and industry sector projections from the IMF, ILO, Euromonitor, and GWI's data and projection model.

GLOBAL WELLNESS INSTITUTE™

Source: https://globalwellnessinstitute.org/press-room/press-releases/globalwellnesseconomymonitor2023/

Who Will Care for Older Adults? We've Plenty of Know-How but Too Few Specialists

Judith Graham, *KFF Health News*, Nov 10, 2023 (excerpt)

Thirty-five years ago, Jerry Gurwitz was among the first physicians in the United States to be credentialed as a geriatrician — a doctor who specializes in the care of older adults.

"I understood the demographic imperative and the issues facing older patients," Gurwitz, 67 and chief of geriatric medicine at the University of Massachusetts Chan Medical School, told me. "I felt this field presented tremendous opportunities."

But today, Gurwitz fears geriatric medicine is on the decline. Despite the surging older population, there are fewer geriatricians now (just over 7,400) than in 2000 (10,270), he noted in a recent piece in JAMA. (In those two decades, the population 65 and older expanded by more than 60%.) Research suggests each geriatrician should care for no more than 700 patients; the current ratio of providers to older patients is 1 to 10,000.

The implications are stark: Geriatricians will be unable to meet soaring demand for their services as the aged U.S. population swells for decades to come. There are just too few of them. "Sadly, our health system and its workforce are wholly unprepared to deal with an imminent surge of multimorbidity, functional impairment, dementia and frailty," Gurwitz warned in his JAMA piece.

This is far from a new concern. Fifteen years ago, a report from the National Academies of Sciences, Engineering, and Medicine concluded: "Unless action is taken immediately, the health care workforce will lack the capacity (in both size and ability) to meet the needs of older patients in the future." According to the American Geriatrics Society, 30,000 geriatricians will be needed by 2030 to care for frail, medically complex seniors.

What's hobbled progress? Gurwitz and fellow physicians cite a number of factors: low Medicare reimbursement for services, low earnings compared with other medical specialties, a lack of prestige, and the belief that older patients are unappealing, too difficult, or not worth the effort.

"There's still tremendous ageism in the health care system and society," said geriatrician Gregg Warshaw, a professor at the University of North Carolina School of Medicine.

But this negative perspective isn't the full story. In some respects, geriatrics has been remarkably successful in disseminating principles and practices meant to improve the care of older adults.

Source: https://kffhealthnews.org/news/article/who-will-care-for-older-adults-weve-plenty-of-know-how-but-too-few-specialists/

Activist Investor Elliott Targets Drugmaker BioMarin

Svea Herbst-Bayliss, *Reuters*, November 7, 2023

NEW YORK, Nov 7 (Reuters) - Activist investor Elliott Investment Management has built a stake in BioMarin Pharmaceutical (BMRN.O) and has been in discussions with the biotechnology company for months about its future, according to two people familiar with the matter.

The hedge fund, which oversees some $60 billion in assets, has spent over $1 billion on the stake in BioMarin, which focuses on rare genetic disorders and is valued at about $16 billion, the sources said.

The nature of the conversations between San Rafael, California-based BioMarin and Elliott, which is headquartered in West Palm Beach, Florida, and any demands the hedge fund may have made could not be learned.

Elliott declined to comment, while a representative for BioMarin did not immediately respond to a request for comment.

BioMarin shares rose 12% to $85.36 on the news in morning trading in New York on Tuesday.

BioMarin is trying to find its footing amid a change in chief executives and slow progress in the launch of its drug Roctavian to treat hemophilia.

After the company last week lowered its 2023 guidance for Roctavian, some analysts cut sales forecasts for the coming years, even though they still see the drug hitting blockbuster status of $1 billion annually in the long run.

Source: https://www.reuters.com/markets/us/activist-investor-elliott-targets-drugmaker-biomarin-sources-2023-11-07/

Does BioMarin's CEO Shuffle Signal Bigger Changes Ahead?

Meaghan Parrish, *Pharmavoice*, Nov 9, 2023

Although BioMarin has notched notable wins in the last few years, its launch of Roctavian, which won EU approval in August 2022 and an FDA nod in June, hasn't hit the heights the company expected. In April, BioMarin predicted the therapy would rake in $50 to $150 million, but payer challenges have dogged its uptake. Eight months after gaining approval in Europe, Roctavian had yet to be taken by a single patient. And in the U.S., payer negotiations for the $2.9 million dollar therapy have also slowed its launch. Ultimately, Roctavian made under $1 million in the third quarter and BioMarin now estimates that it'll make less than $10 million this year.

In its statement announcing the leadership change, BioMarin noted that Hardy has 30 years of experience in global healthcare and that as CEO of Genentech, he "demonstrated the ability to deliver growth during a particularly challenging period."

Alexander Hardy, New CEO, BioMarin

Source: https://www.pharmavoice.com/news/biomarin-ceo-genentech-jean-jacques-bienaime/699378/

Novo Nordisk Invests More Than 42 Billion Danish Kroner in Expansion of Manufacturing Facilities in Kalundborg, Denmark

Bagsværd, Denmark, 10 November 2023 – Novo Nordisk today announced plans to invest more than 42 billion Danish kroner starting in 2023 to expand existing manufacturing facilities in Kalundborg, Denmark, for the current and future product portfolio within serious chronic diseases.

The investment comes as Novo Nordisk marks the 100th anniversary of its founding in Denmark, where more than 23,000 employees still work today. Most of these employees work at production sites.

The investment will create additional capacity across the entire global value chain from manufacturing of active pharmaceutical ingredients (API) to packaging, with the vast majority invested in API capacity. The new API facility will be designed as a multi-product facility, with flexibility to accommodate current and future processes. The investment, which includes GLP-1 products, will increase Novo Nordisk's ability to meet future market demands.

"The significant investment announced today confirms the importance of utilising our existing sites, including in Denmark, as cornerstones for not only the growth we see but also to expand as fast as possible by utilising all the infrastructure, knowledge and competences we already have," said Henrik Wulff, executive vice president, Product Supply, Quality & IT, Novo Nordisk. "Our continued investment in global capacity demonstrates the belief we have in our current and future product portfolio and its relevance for people living with serious chronic diseases."

The new API facility will have a footprint of 170,000 m2. It will be designed as a multi-product facility with flexibility to accommodate future processes and displaying state-of-the-art technology and working environment. As a future-proof and cost-effective facility, the construction will focus on delivering the highest quality to patients globally in an efficient and environmentally sustainable way2.

The construction projects will be finalised gradually from the end of 2025 through 2029. The projects are expected to create 8003 new jobs in the facilities when construction is completed, and the facilities are fully equipped. During the construction phase, up to 3,000 external employees will be employed.

Over the past two years, Novo Nordisk has announced 40 billion Danish kroner in production investments in Denmark. Novo Nordisk has also added approximately 1,100 employees in production related to these investments. Earlier this year, Novo Nordisk confirmed that it awaits approvals for a new production site on Funen, Denmark.

Source: https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166342

Rendering of Added Buildings in Novo Site in Kalundborg, Denmark, Nov 10, 2023

BCG Study: Bringing Advanced Diagnostics to Market

Kristen Cook, Shashanka Muppaneni, Johannes Thoms, David Tompkins, and Maximilian Roth, BCG, Nov 9, 2023 (excerpt)

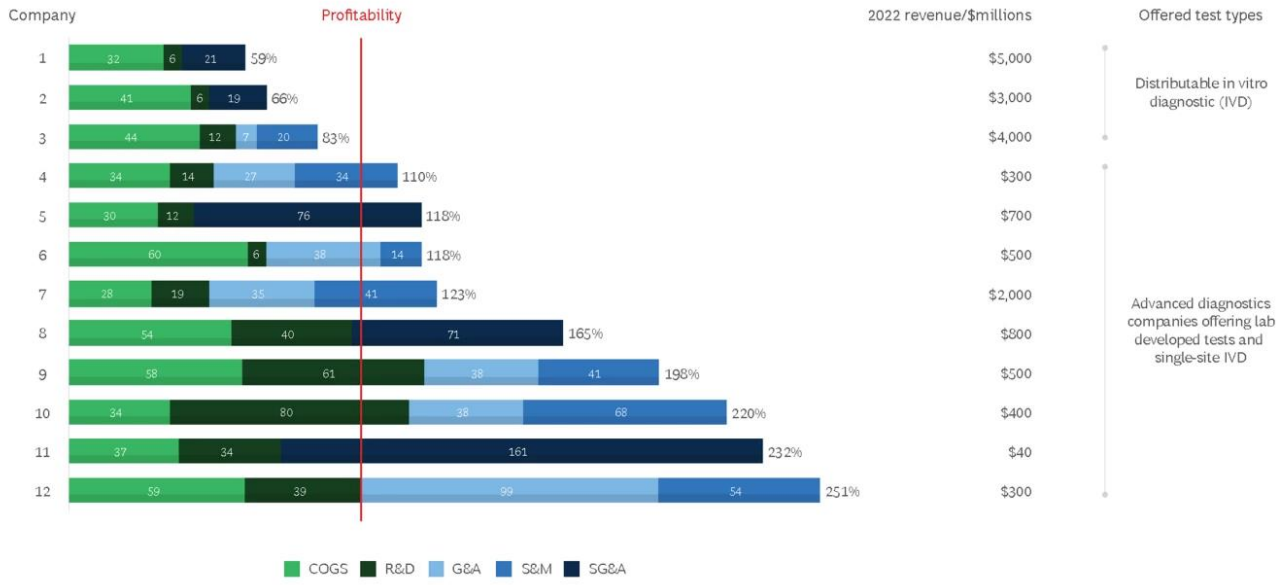
The potential of advanced diagnostic tests to address unmet patient needs is growing rapidly as genomics, proteomics, and other technologies fuel biomarker discovery and deepen understanding of disease pathways. Yet BCG analysis has found that few advanced diagnostics companies turned a profit last year. (See Exhibit 1.)

The success of any advanced diagnostic, of course, depends heavily on the commercialization efforts behind it, with significant sustained investment over many years and often periods of negative profitability. For example, for select companies with on-market products earning more than $100 million in revenue, the combined cost of R&D (including clinical evidence generation) and sales and marketing can surpass 100% of revenue.

In our experience, when it comes to launching laboratory-developed tests (LDTs) or in vitro diagnostics (IVD) in the US, or IVDR (IVD regulation compliant) tests in Europe, companies should pursue a commercialization strategy focusing on three major imperatives: proving actionability, establishing access, and expanding adoption. Although each requires much in the way of capabilities, resources, and time, together they can set the foundation for successful market adoption and sustained growth.

Exhibit 1 - R&D and Sales & Marketing Can Exceed 100% of Revenue

Advanced Diagnostics Companies' Costs as % of Revenue, 2022



Source: BCG analysis.

Note: This is an illustrative, nonexhaustive representation of costs. COGS =cost of goods sold; S&M =sales & marketing; G&A =general & administrative; SG&A =selling, general & administrative.

Source: https://www.bcg.com/publications/2023/bringing-advanced-diagnostic-testing-to-market

Andrew Pannu Compares Analyst Forecast to Actual Five Years Later

5-Year Projections vs. Actual Performance for Select New Drugs

Class of 2013					Class of 2014					Class of 2015				
Drug	Company	2018E	2018A	Variance	Drug	Company	2019E	2019A	Variance	Drug	Company	2020E	2020A	Variance
Sovaldi	Gilead	$7,250	$250	(96.6%)	Opdivo	BMS	$3,500	$7,204	105.8%	Tecentriq	Roche	$4,750	$2,920	(38.5%)
Opdivo	BMS	$2,000	$6,735	236.8%	Garsadil 9	Merck	$2,100	$3,737	78.0%	Imfinzi	AstraZeneca	$2,515	$2,042	(18.8%)
Anoro Ellipta	GSK / THRX	$1,960	$1,733	(11.6%)	Ibrance	Pfizer	$2,000	$4,961	148.1%	Venclexta	AbbVie	$2,000	$1,337	(33.2%)
HCV Combos	AbbVie	$1,000	$3,616	261.6%	Venclexta	AbbVie	$1,500	$792	(47.2%)	Darzalex	J&J	$1,250	$4,190	235.2%
Keytruda	Merck	$1,000	$7,171	617.1%	HCV Combos	AbbVie	$1,200	$2,893	141.1%	Anacetrapib	Merck	$1,200	–	(100.0%)
Ibrance	Pfizer	$1,000	$4,118	311.8%	Entresto	Novartis	$1,000	$1,726	72.6%	Spravato	J&J	$1,000	N/A	N/A
Cyramza	Eli Lilly	$800	$821	2.7%	Darzalex	J&J	$900	$2,998	233.1%	Kisqali	Novartis	$1,000	$687	(31.3%)
Cerdelga	Sanofi	$800	$188	(76.5%)	Anacetrapib	Merck	$900	–	(100.0%)	Shingrix	GSK	$785	$2,553	225.3%
Anacetrapib	Merck	$600	–	(100.0%)	Praluent	Sanofi	$775	$289	(62.7%)	Orilissa	AbbVie	$700	$125	(82.1%)
Odanacatib	Merck	$600	–	(100.0%)	Trumenba	Pfizer	$550	$17	(96.9%)	Sirukumab	J&J	$650	–	(100.0%)
Total		**$17,010**	**$24,632**	**44.8%**	**Total**		**$14,425**	**$24,617**	**70.7%**	**Total**		**$15,850**	**$13,854**	**(12.6%)**

Class of 2016					Class of 2017					Class of 2018				
Drug	Company	2021E	2021A	Variance	Drug	Company	2022E	2022A	Variance	Drug	Company	2023E	2023 RR	Variance
Ocrevus	Roche	$4,000	$5,510	37.7%	Erleada	J&J	$1,350	$1,881	39.3%	Evrysdi	Roche	$1,735	$1,590	(8.3%)
Imfinzi	AstraZeneca	$3,080	$2,412	(21.7%)	Hemlibra	Roche	$1,000	$3,976	297.6%	Rinvoq	AbbVie	$1,600	$3,619	126.2%
Dupixent	Sanofi	$1,855	$6,210	234.7%	Calquence	AstraZeneca	$1,000	$2,057	105.7%	Zolgensma	Novartis	$1,500	$1,237	(17.5%)
Verzenio	Eli Lilly	$1,800	$1,350	(25.0%)	Sirukumab	J&J	$950	–	(100.0%)	Skyrizi	AbbVie	$1,400	$7,159	411.3%
Solanezumab	Eli Lilly	$1,500	–	(100.0%)	Orilissa	AbbVie	$800	$165	(79.3%)	Beovu	Novartis	$1,000	$201	(79.9%)
Tremfya	J&J	$1,450	$2,127	46.7%	Fasenra	AstraZeneca	$700	$1,396	99.4%	Imjudo	AstraZeneca	$900	N/A	N/A
Eucrisa	Pfizer	$1,000	$115	(88.5%)	Anacetrapib	Merck	$600	–	(100.0%)	Beovu	Novartis	$1,000	$201	(79.9%)
Shingrix	GSK	$985	$2,358	139.4%	Kymriah	Novartis	$600	$536	(10.7%)	Raylumis	Pfizer	$400	–	(100.0%)
Sirukumab	J&J	$950	–	(100.0%)	Lampalizumab	Roche	$600	–	(100.0%)	Mayzent	Novartis	$400	$381	(4.7%)
Calquence	AstraZeneca	$920	$1,238	34.6%	Verubecestat	Merck	$500	–	(100.0%)	Blenrep	GSK	$325	$17	(94.9%)
Total		**$17,540**	**$21,319**	**21.5%**	**Total**		**$8,100**	**$10,011**	**23.6%**	**Total**		**$10,260**	**$14,406**	**40.4%**

Note: sales estimates represent sell-side views

(1) Converted to USD at average exchange rate for that year; (2) Estimated; (3) Unavailable, but far below estimate given launch difficulties; only started to pick up in 2022; (4) Unavailable, but far below estimate given only approved in Q4'22

Andrew Pannu @andrewpannu

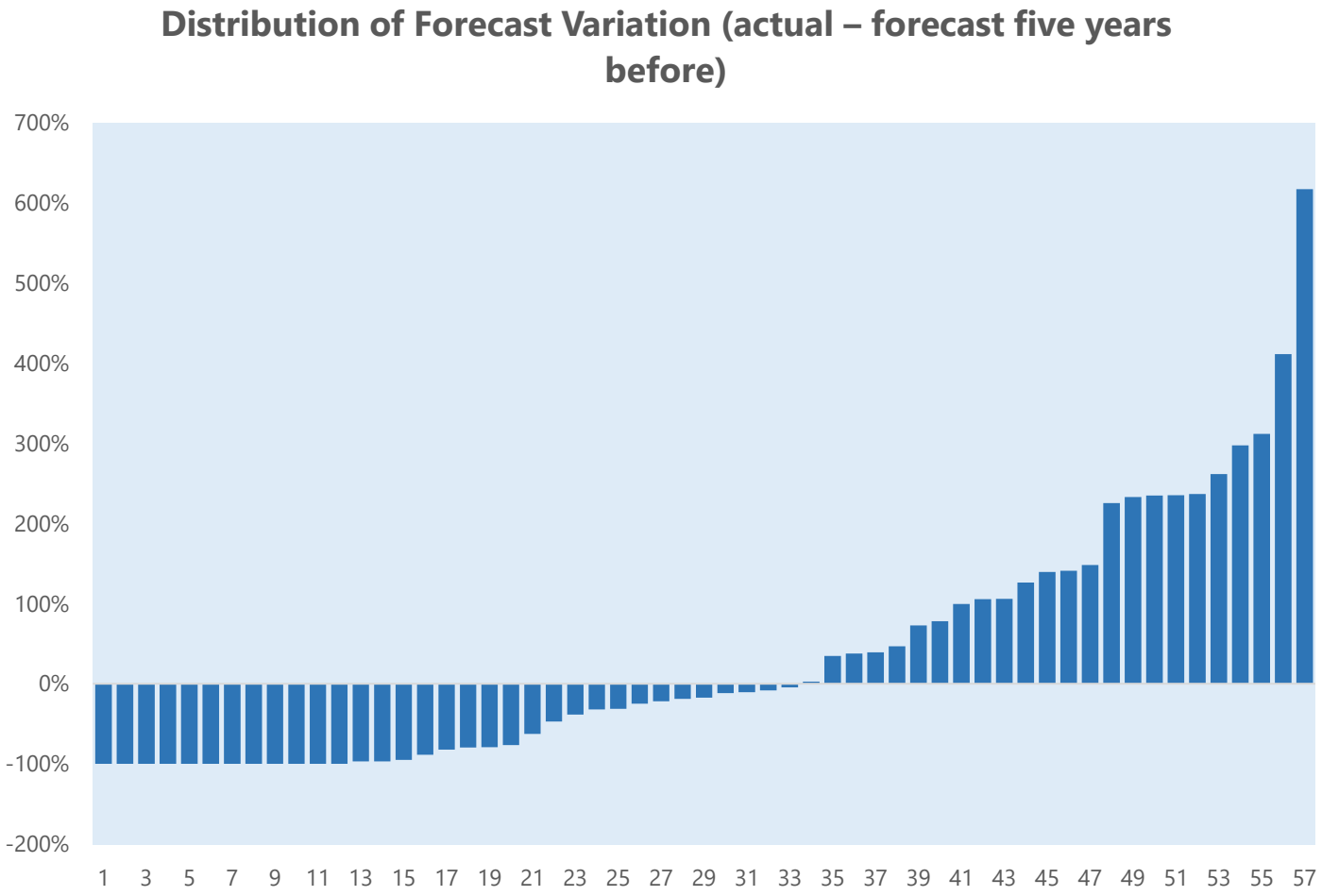
This is a really interesting analysis performed by the ever-thoughtful Andrew Pannu.

It suggests that analyst revenue forecasts are typically quite wrong.

We performed a similar exercise in 2004 and found a very similar result.

Source: https://twitter.com/andrewpannu

Distribution of Forecast Outcomes from Pannu Analysis



1. On average, forecasts are wrong. Only 7 of 57 were within 20% of actual.
2. The median forecast variance was -18% (that is, actual was 18% below forecast).
3. 58% of forecasts were too high.
4. The average forecast variance was 35% (drugs, on average do better as there is a long tail on the right side of the distribution).
5. One interesting fact is that the median variance for biologics is positive, and the average variance was 71%. Analysts tend to underestimate "big biologics" like Darzalex, Keytruda etc. and tend to overestimate potential of small molecules.

Source: Stifel analysis of Pannu data.

PERSPECTIVE

Use of GPT-4 to Diagnose Complex Clinical Cases

Alexander V. Eriksen, M.D.,[1,2] Sören Möller, M.Sc., Ph.D.,[3,4] and Jesper Ryg, M.D., Ph.D.[1,2]

Received: July 10, 2023; Revised: September 15, 2023; Accepted: September 29, 2023; Published: November 9, 2023

"We assessed the performance of the newly released AI GPT-4 in diagnosing complex medical case challenges and compared the success rate to that of medical-journal readers. GPT-4 correctly diagnosed 57% of cases, outperforming 99.98% of simulated human readers generated from online answers. We highlight the potential for AI to be a powerful supportive tool for diagnosis; however, further improvements, validation, and addressing of ethical considerations are needed before clinical implementation."

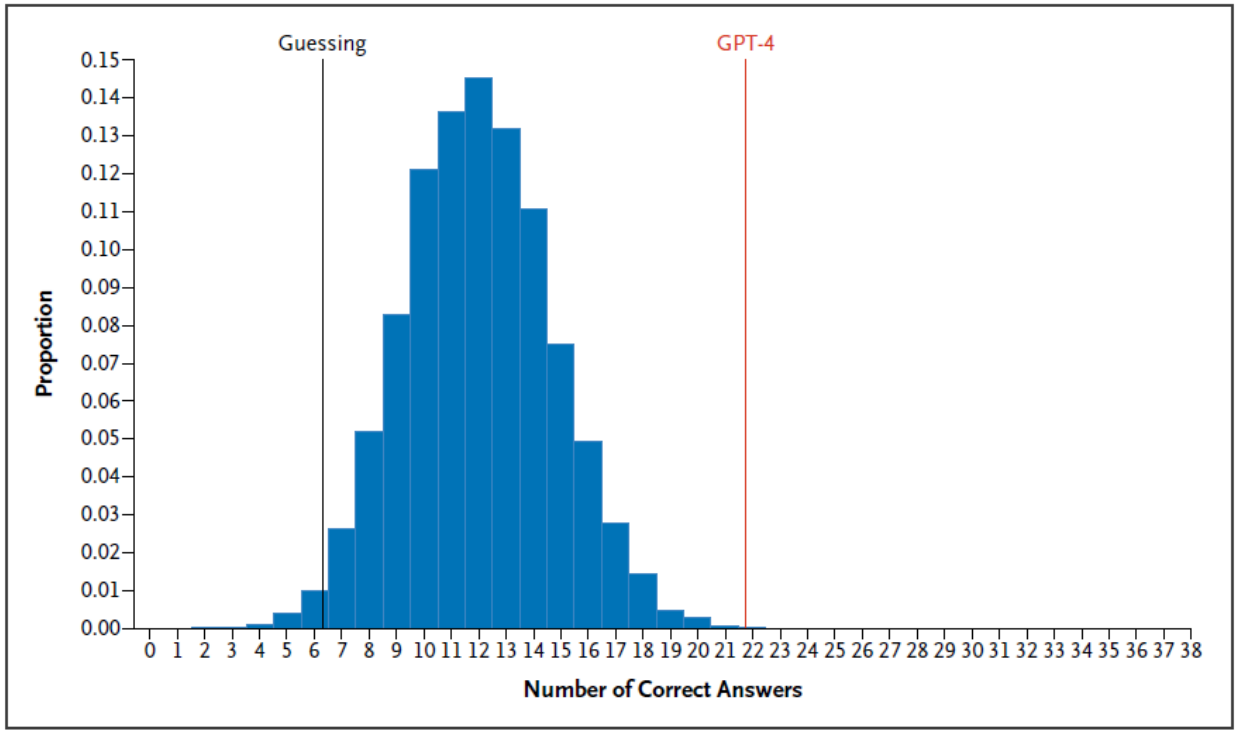


Figure 1. Number of Correct Answers of GPT-4 Compared with Guessing and a Simulated Population of Medical-Journal Readers.

Number of correct answers of GPT-4 (red line) to 38 multiple-choice real-world clinical case challenges compared with what would be expected by purely guessing with uniform probability for all answer possibilities (black line) and to the proportion of correct answers by a simulated population of 10,000 medical-journal readers (blue histogram).

Source: https://ai.nejm.org/content/early-release-articles

BioNTech Highlights Impressive AI Capabilities

Our AI Capabilities

300+ AI Experts

From AI researchers to ML engineers and ML Ops experts, our team has critical size, depth, and a differentiated ability to attract talents in EMEA.

Supercomputing Assets

Our proprietary GPU cluster in the UK (500 petaflops expected 2024), is optimized for high performance computing and fully managed by our Aichor software platform.

AI Research Capabilities

Strong contributor to major AI conferences (NeurIPS, ICLR etc.), workshops and journals.
25 publications in 2023, in ML for Biology and AI Decision-Making.

Frontier LLMs

Proprietary high-efficiency libraries for advanced Large Language Model (LLM) training, supporting R&D efforts and biology-focused generative AI.

Large Scale Optimization

Distributed, scalable reinforcement Learning (RL) and combinatorial optimization algorithms. 5 reference JAX frameworks released.

Quantum Machine Learning

Pioneer in Quantum Machine Learning incl. publications in Nature journals, collaborations (NPL, Cambridge, IBM) and commercial partnerships.

Software Productization

Converting technology powered by our AI innovation into user-friendly, scalable software products integrated with our compute infrastructure and the Cloud.

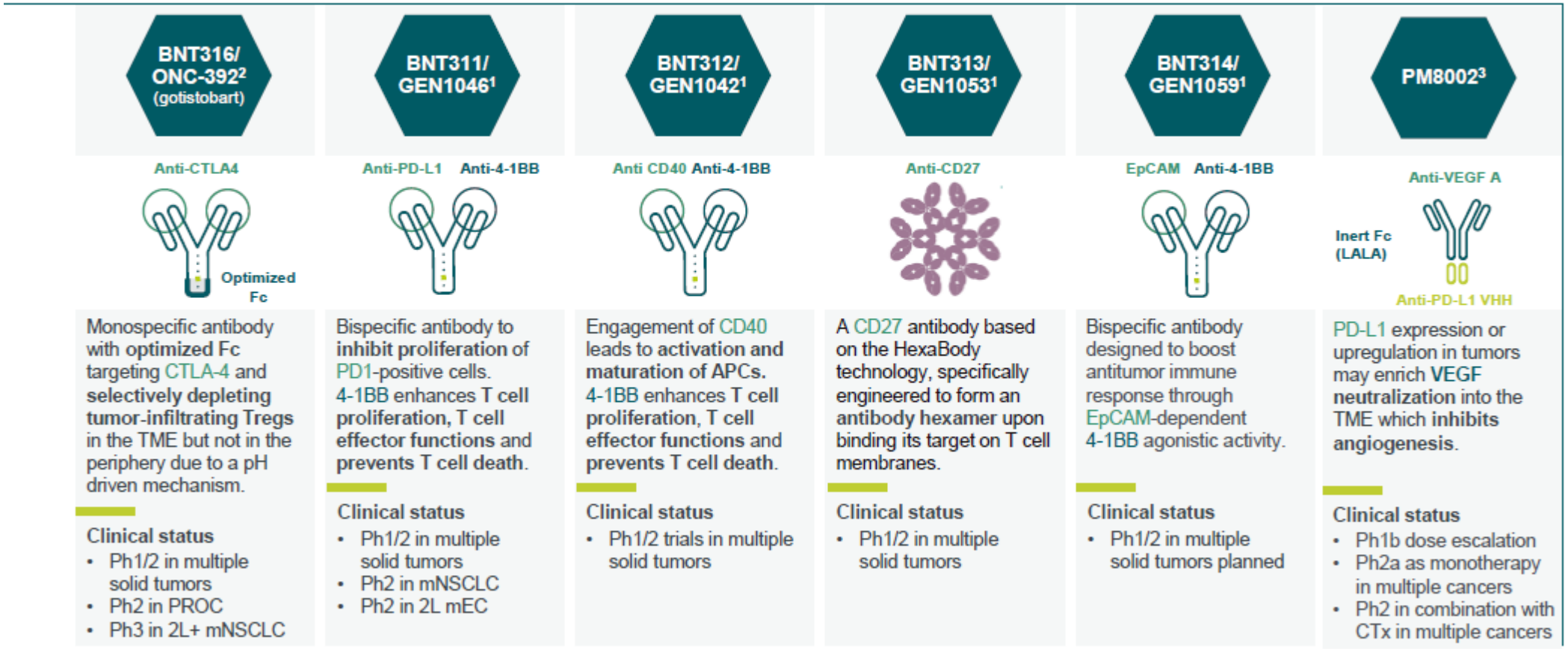
Simulation Expertise

Physically realistic representations of complex environments, optimized for speed, including GPU-accelerated Molecular Dynamics in biology.

AI = artificial intelligence; ML = machine learning; EMEA = Europe, Middle East, India & Africa; GPU = Graphics Processing Unit; NeurIPS = Neural Information Processing System; ICLR = International Conference on Learning Representations; NPL = National Physical Laboratory.

BioNTech Has Vast Pipeline Including Items in IO

Well-Positioned in Immuno-Oncology with Therapeutic Candidates Across Multiple Tumors



1. Partnered with Genmab; 2. Partnered with OncoC4; 3. Partnered with Biotheus. CTLA4 = Cytotoxic T-Lymphocyte-Associated Protein 4; CD27, CD40, 4-1BB = members of the tumor necrosis factor receptor superfamily; PD-1 =Programmed cell death protein 1; HER2 = human epidermal growth factor receptor 2; ADCC = Antibody dependent cell-mediated cytotoxicity; ADCP = Antibody dependent cellular phagocytosis; PROC = platinum-resistant ovarian cancer; NSCLC = non-small cell lung cancer; EC = endometrial cancer APC = antigen presenting cells; VEGF = vascular endothelial growth factor; TME = tumor microenvironment; CTx = chemotherapy; LALA = IgG1 variant L234A/L235A.

BIONTECH

Alnylam Presents Positive Results from the KARDIA-1 Phase 2 Dose-Ranging Study of Zilebesiran, an Investigational RNAi Therapeutic in Development for the Treatment of Hypertension in Patients at High Cardiovascular Risk

November 11, 2023 04:00 PM Eastern Standard Time

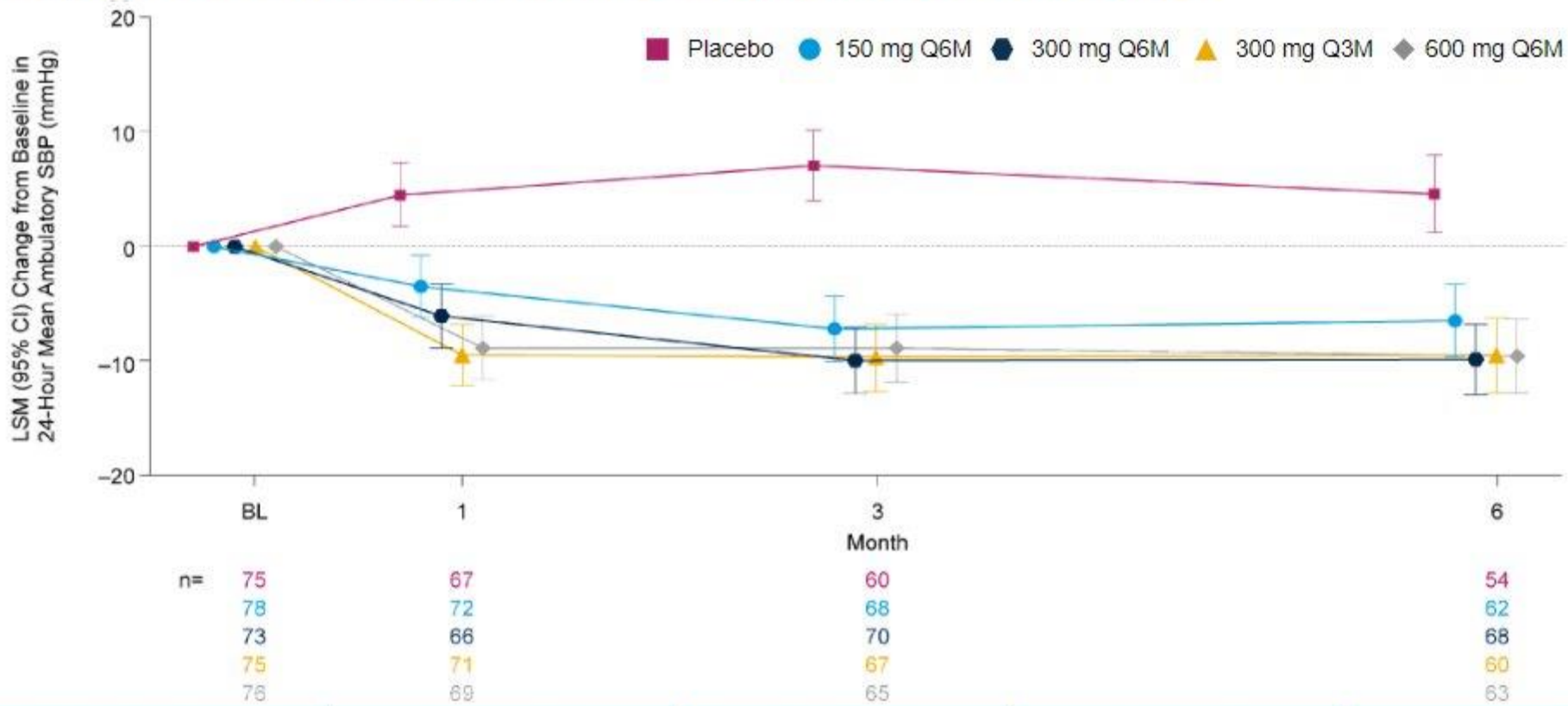
CAMBRIDGE, Mass.--(BUSINESS WIRE)--Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced positive results from the KARDIA-1 Phase 2 study of zilebesiran, an investigational RNAi therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of patients with hypertension and high cardiovascular risk. The study results were presented during the American Heart Association (AHA) Scientific Sessions being held in Philadelphia, Pennsylvania from November 11-13, 2023. The Company previously announced positive topline results from the KARDIA-1 study in September 2023. The KARDIA-1 study achieved its primary endpoint, with single doses of zilebesiran demonstrating clinically significant reductions in 24-hour mean systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring (ABPM) at Month 3 across all doses, with the 150 mg, 300 mg, and 600 mg doses achieving placebo-adjusted reductions of 14.1 mmHg, 16.7 mmHg, and 15.7 mmHg, respectively (all p-values less than 0.0001).

Key Endpoints	150 mg Q6M	300 mg Q6M	300 mg Q3M	600 mg Q6M
Primary Endpoint				
Change from Baseline to Month 3 in 24-Hour Mean Ambulatory SBP	-14.1 mmHg (p less than 0.0001)	-16.7 mmHg (p less than 0.0001) *		-15.7 mmHg (p less than 0.0001)
Key Secondary Endpoints				
Change from Baseline to Month 6 in 24-Hour Mean Ambulatory SBP	-11.1 mmHg (p less than 0.0001)	-14.5 mmHg (p less than 0.0001)	-14.1 mmHg (p less than 0.0001)	-14.2 mmHg (p less than 0.0001)
Change from Baseline to Month 3 in Office SBP	-9.6 mmHg (p less than 0.0001)	-12.0 mmHg (p less than 0.0001) *		-9.1 mmHg (p less than 0.0001)
Change from Baseline to Month 6 in Office SBP	-7.5 mmHg (p=0.0025)	-10.5 mmHg (p less than 0.0001)	-12.1 mmHg (p less than 0.0001)	-10.2 mmHg (p less than 0.0001)

Source: https://www.businesswire.com/news/home/20231111731245/en/Alnylam-Presents-Positive-Results-from-the-KARDIA-1-Phase-2-Dose-Ranging-Study-of-Zilebesiran-an-Investigational-RNAi-Therapeutic-in-Development-for-the-Treatment-of-Hypertension-in-Patients-at-High-Cardiovascular-Risk

Significant Decreases in ABPM SBP with All Zilebesiran Regimens

Change from Baseline to Month 6 in 24-Hour Mean Ambulatory SBP

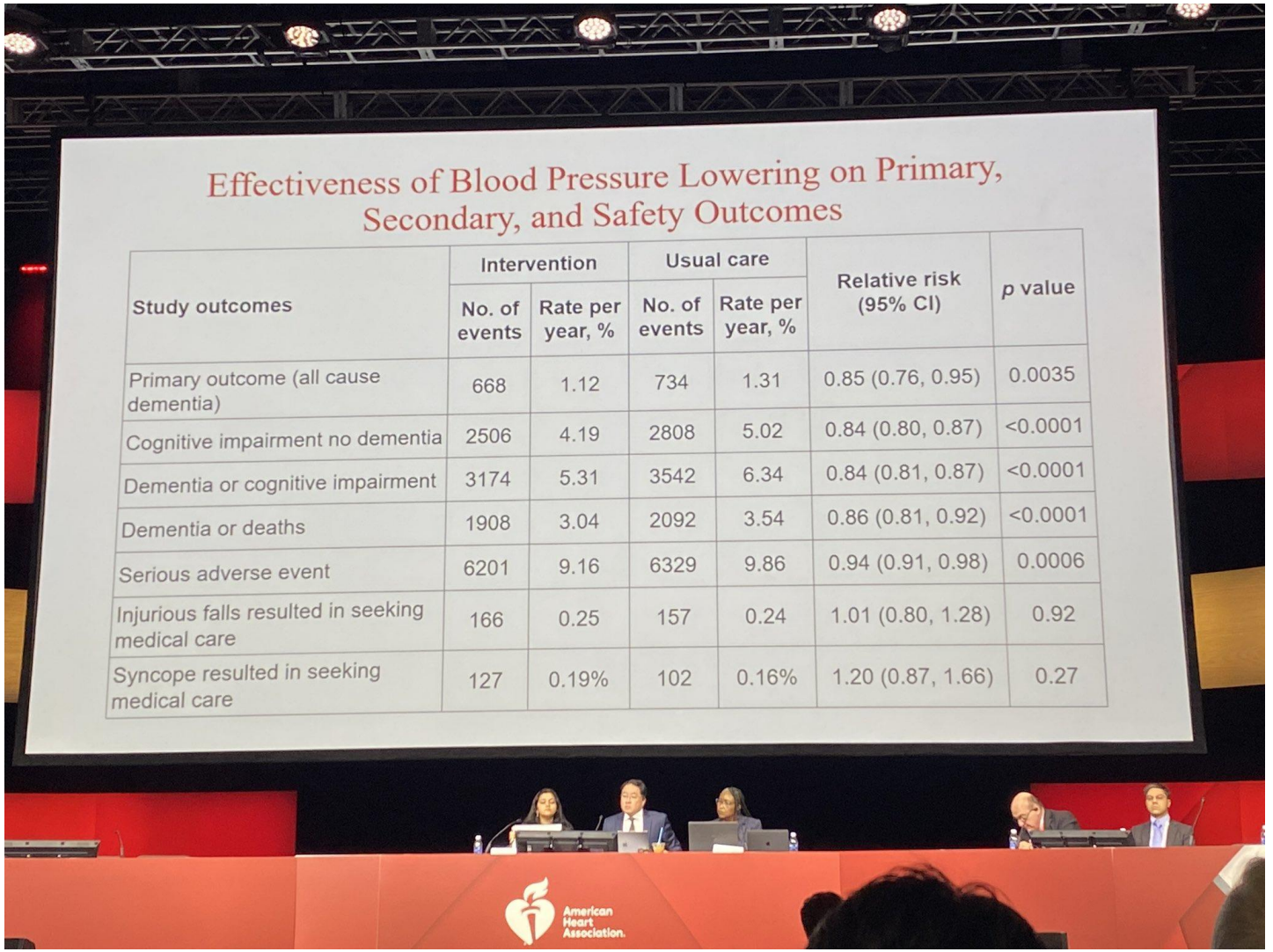


Month 6 (Key Secondary Endpoint)	150 mg Q6M	300 mg Q6M	300 mg Q3M	600 mg Q6M
LSMD vs placebo, mmHg (95% CI)	**−11.1** (−15.8, −6.4), p=4.5E−06	**−14.5** (−19.1, −9.9), p=1.8E−09	**−14.1** (−18.9, −9.4), p=9.1E−09	**−14.2** (−18.9, −9.5), p=5.8E−09

Blood pressure measurements were censored if taken while patients were receiving or within 2 weeks after stopping any rescue medication. *The adjusted 95% CI and *p* value are based on Dunnett's test.

7 ABPM, ambulatory blood pressure monitoring; BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, least-squares mean difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.

Chinese Study at AHA Shows Blood Pressure Lowering Has Major Effect on Dementia and Cognition



Study outcomes	Intervention		Usual care		Relative risk (95% CI)	*p* value
	No. of events	Rate per year, %	No. of events	Rate per year, %		
Primary outcome (all cause dementia)	668	1.12	734	1.31	0.85 (0.76, 0.95)	0.0035
Cognitive impairment no dementia	2506	4.19	2808	5.02	0.84 (0.80, 0.87)	<0.0001
Dementia or cognitive impairment	3174	5.31	3542	6.34	0.84 (0.81, 0.87)	<0.0001
Dementia or deaths	1908	3.04	2092	3.54	0.86 (0.81, 0.92)	<0.0001
Serious adverse event	6201	9.16	6329	9.86	0.94 (0.91, 0.98)	0.0006
Injurious falls resulted in seeking medical care	166	0.25	157	0.24	1.01 (0.80, 1.28)	0.92
Syncope resulted in seeking medical care	127	0.19%	102	0.16%	1.20 (0.87, 1.66)	0.27

Source: https://twitter.com/TheDawnBell

Celldex Therapeutics Announces Positive Topline Results from Barzolvolimab Phase 2 Study in Chronic Spontaneous Urticaria

HAMPTON, N.J., Nov. 06, 2023 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. (NASDAQ:CLDX) announced today positive topline results from the Company's Phase 2 clinical trial of barzolvolimab in patients with moderate to severe chronic spontaneous urticaria (CSU) refractory to antihistamines, including patients who received prior biologics. Barzolvolimab is a humanized monoclonal antibody that specifically binds the receptor tyrosine kinase KIT with high specificity and potently inhibits its activity, which is required for mast cell function and survival. CSU is characterized by the occurrence of hives or wheals for 6 weeks or longer without identifiable specific triggers or causes. Treatment options for patients with CSU are limited and there are no approved therapies for patients who do not respond to omalizumab.

Data from the 208 patients randomized in the study showed that barzolvolimab achieved the primary efficacy endpoint, with a statistically significant mean change from baseline to week 12 of UAS7 (urticaria activity score) compared to placebo. Barzolvolimab demonstrated rapid, durable and clinically meaningful responses in patients with moderate to severe CSU refractory to antihistamines, including patients with prior omalizumab treatment.

Summary of Clinical Activity Assessments at Week 12				
	300 mg q8w (n=51)	150 mg q4w (n=52)	75 mg q4w (n=53)	Placebo (n=51)
UAS7 Changes				
Baseline UAS7 (mean)	31.33	30.75	30.30	30.09
LS Mean change at Week 12	-23.87	-23.02	-17.06	-10.47
LS Mean difference from placebo (Confidence Interval, p value)	-13.41 (CI: -17.47, -9.34) **p<0.0001**	-12.55 (CI:-16.56, -8.55) **p<0.0001**	-6.60 (CI:-10.71, -2.49) p=0.0017	
Clinical Responses				
UAS7=0 (Complete Control)	37.5%	51.1%	22.9%	6.4%
UAS7≤6 (Well-controlled)	62.5%	59.6%	41.7%	12.8%

Approximately 20% of enrolled patients received prior treatment with omalizumab. These patients experienced a similar clinical benefit as the overall treated population within their individual dosing groups.

Celldex stock jumped 29% on this data. Note: Barzolvolimab is a humanized monoclonal antibody that specifically binds the receptor tyrosine kinase KIT with high specificity and potently inhibits its activity, which is required for mast cell function and survival.

Source: https://ir.celldex.com/news-releases/news-release-details/celldex-therapeutics-announces-positive-topline-results

Neurocrine Biosciences Provides Development Pipeline Update

Phase 2 Proof-of-Concept Study of NBI-921352 in Patients with Focal Onset Seizures Failed to Demonstrate Meaningful Reduction in Seizure Frequency

Phase 2 Proof-of-Concept Study of NBI-1065846 in Patients with Anhedonia in Major Depressive Disorder Failed to Meet its Primary Endpoint

SAN DIEGO, Nov. 9, 2023 /PRNewswire/ -- Neurocrine Biosciences, Inc. (Nasdaq: NBIX), a leading neuroscience-focused biopharmaceutical company, today announced Phase 2 study results from two signal-seeking pipeline programs in focal onset seizures and anhedonia.

Epilepsy Update: The investigational selective **NaV 1.6 inhibitor**, NBI-921352, licensed from Xenon Pharmaceuticals, Inc. (Xenon), failed to demonstrate meaningful seizure frequency reduction in the Phase 2 dose finding study assessing the safety, efficacy, tolerability and pharmacokinetics as adjunctive therapy in adults with focal onset seizures. No further development with NBI-921352 in Focal Onset Seizure (FOS) is planned at this time. Neurocrine is reviewing the data from the FOS study to understand any potential implication for its ongoing study in SCN8A-developmental epileptic encephalopathy and will provide an update once this review is complete. The company continues to advance a pre-clinical dual NaV1.2/1.6 inhibitor as part of the Xenon collaboration.

Psychiatry Update: The investigational NBI-1065846, as part of the collaboration with Takeda Pharmaceutical Company Limited (Takeda), did not meet its primary endpoint in the Phase 2 TERPSIS™ study evaluating its efficacy compared to placebo in patients with anhedonia in major depressive disorder. No further development with NBI-1065846 is planned at this time. Neurocrine and Takeda continue to collaborate on several programs in clinical development including NBI-1065845 for the treatment of inadequate response to treatment in major depressive disorder (Phase 2), luvadaxistat for the treatment of cognitive impairment associated with schizophrenia (Phase 2), and NBI-1070770 for the treatment of major depressive disorder (Phase 1).

Source: https://www.prnewswire.com/news-releases/neurocrine-biosciences-provides-development-pipeline-update-301983959.html

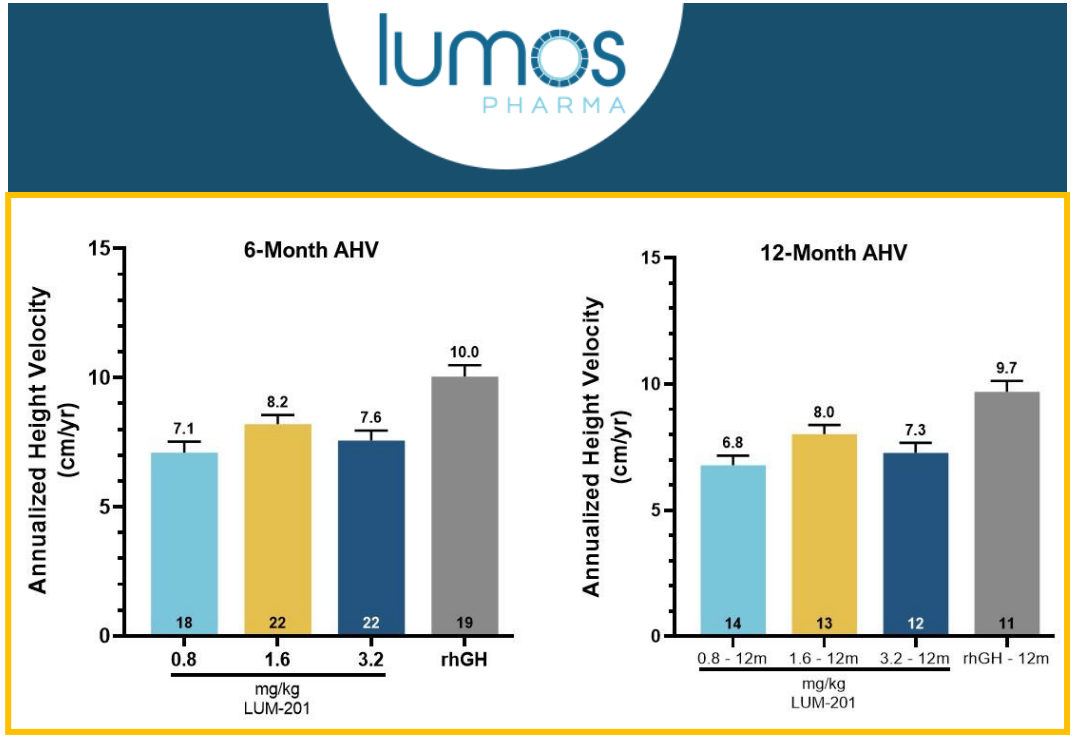
Lumos Pharma Announces Topline Data from Phase 2 OraGrowtH210 and OraGrowtH212 Trials of LUM-201 in PGHD Met All Primary and Secondary Endpoints

AUSTIN, Texas, Nov. 07, 2023 (GLOBE NEWSWIRE) -- Lumos Pharma, Inc. (NASDAQ:LUMO) today announced that topline results from its Phase 2 OraGrowtH210 dose-finding trial and its Phase 2 OraGrowtH212 Pharmacokinetic/Pharmacodynamic (PK/PD) trial met all primary and secondary endpoints.

Data from the OraGrowtH210 Trial demonstrated annualized height velocity (AHV) on the 1.6 mg/kg dose of orally administered LUM-201 of 8.2 cm/yr at six months and 8.0 cm/yr at 12 months on treatment, in line with historical data in moderate pediatric growth hormone deficiency (PGHD) patients and within the targeted 2 cm/yr margin of the comparator injectable recombinant growth hormone (rhGH) arm. Data also provided preliminary validation of the predictive enrichment marker (PEM) strategy, with prespecified primary and secondary outcomes met, de-risking our patient selection for our Phase 3 program.

Data from the OraGrowtH212 Trial confirmed that LUM-201's unique pulsatile mechanism produces an increase in growth rates while restoring growth hormone secretion and IGF-1 to within normal ranges †, with levels substantially below those produced by exogenous injectable rhGH.†† Additionally, data from a small subset of 10 subjects combined 1.6 and 3.2 mg/kg dosage of LUM-201 in both OraGrowtH210 and OraGrowtH212 trials demonstrated the sustained effectiveness of AHV up to 24 months. Furthermore, the safety profile for LUM-201 remained clean throughout both Phase 2 studies, with no safety concerns identified in either of our Phase 2 trials conducted thus far.

Lumos Pharma shares doubled last week on news that their oral growth hormone product came very close to injectable growth hormone in height growth velocity in children.



Source: https://investors.lumos-pharma.com/news-releases/news-release-details/lumos-pharma-announces-topline-data-phase-2-oragrowth210-and

Ventyx to Terminate its Psoriasis Program After Disappointing Clinical Studies

VENTYX BIOSCIENCES ANNOUNCES RESULTS FROM THE PHASE 2 TRIAL OF VTX958 IN PATIENTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS AND PROVIDES CORPORATE UPDATE

NOVEMBER 6, 2023

PDF VERSION

VTX958 225 mg BID and 300 mg BID doses achieved statistical significance on the primary endpoint (PASI 75) and all key secondary endpoints at Week 16

Efficacy results did not meet the internal target to support further development of VTX958 in psoriasis; Ventyx to terminate Phase 2 trials of VTX958 in plaque psoriasis and psoriatic arthritis

The ongoing Phase 2 trial of VTX958 in Crohn's disease will continue to enroll; Ventyx intends to conduct an interim efficacy analysis in Q1 2024

Cash, cash equivalents and marketable securities of $300.8M as of September 30, 2023

Ventyx to host conference call and webcast today at 4:30 PM ET

SAN DIEGO, Nov. 06, 2023 (GLOBE NEWSWIRE) -- Ventyx Biosciences, Inc. (Nasdaq: VTYX) ("Ventyx"), a clinical-stage biopharmaceutical company focused on advancing novel oral therapies that address a broad range of inflammatory diseases with significant unmet medical need, today announced results from the Phase 2 trial of VTX958 in patients with moderate to severe plaque psoriasis and provided a corporate update.

"While the Phase 2 trial of VTX958 in plaque psoriasis met the primary and key secondary endpoints, we are disappointed by the magnitude of efficacy observed, despite having achieved target levels of drug exposure in the trial," said Raju Mohan, Ph.D., Founder and Chief Executive Officer. "Although these results do not support

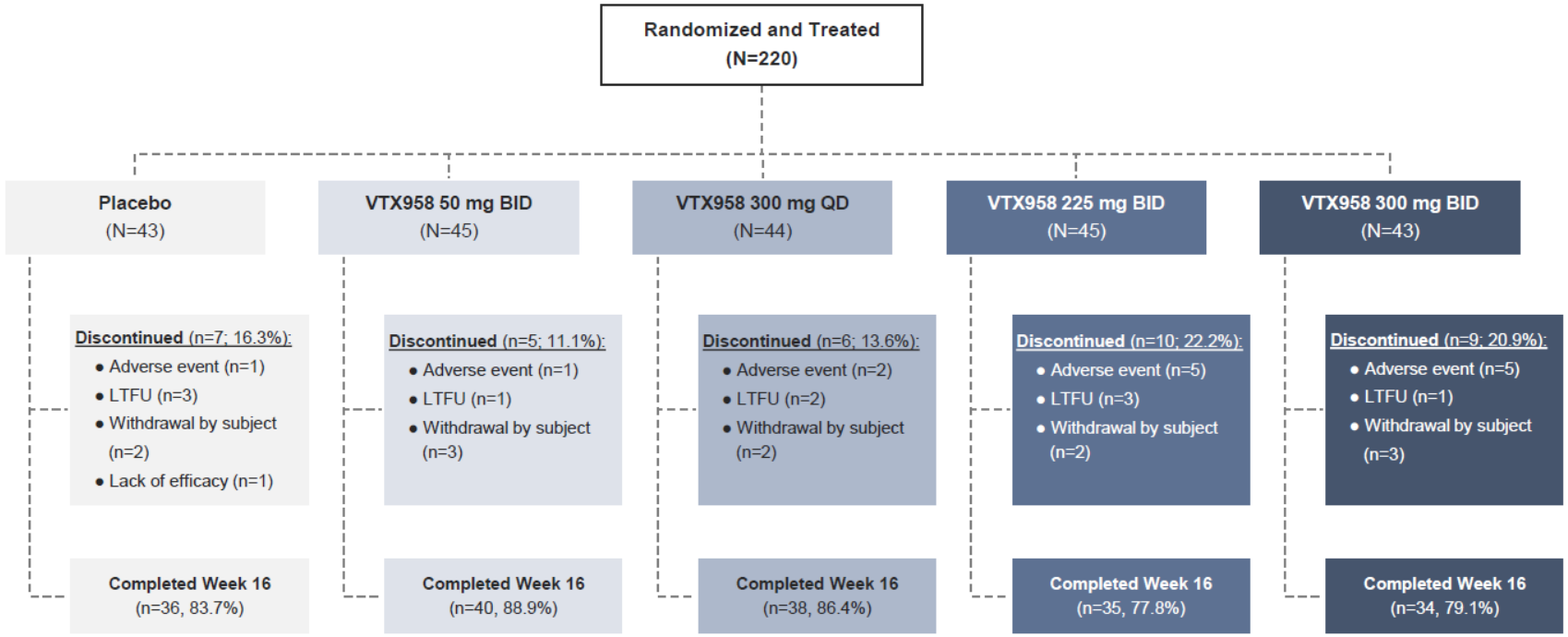
Source: https://ir.ventyxbio.com/news-releases/news-release-details/ventyx-biosciences-announces-results-phase-2-trial-vtx958

ventyx BIOSCIENCES

The Ventyx data for VTX958 in psoriasis were definitely not good. The company ended up seeing its share drop from over $14 a share to $2.72. The cash value of the company is close to $6 a share and there remains a highly attractive NLRP3 in development. We have argued in past reports that the market appears to be overreacting to bad news and underreacting to good news. Last week's experience appears to be in line with this pattern.

Ventyx TYK2 Study

Participant Disposition



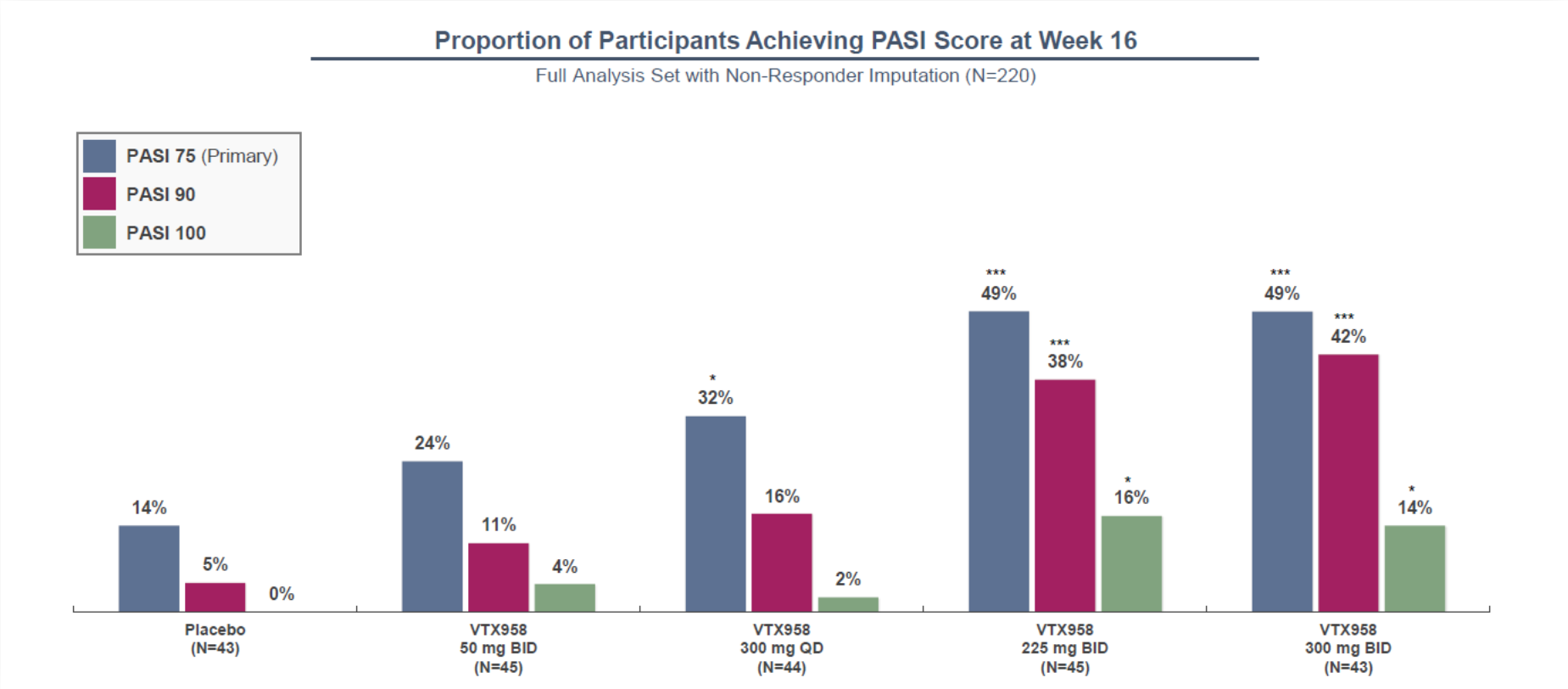
Somewhat higher discontinuation rates at the two higher BID doses than with placebo.

LTFU: Lost to follow up; BID: twice daily; QD: once daily. Source: Ventyx data on file.

Ventyx TYK2 Study

Proportion of Participants Achieving PASI 75, 90, and 100

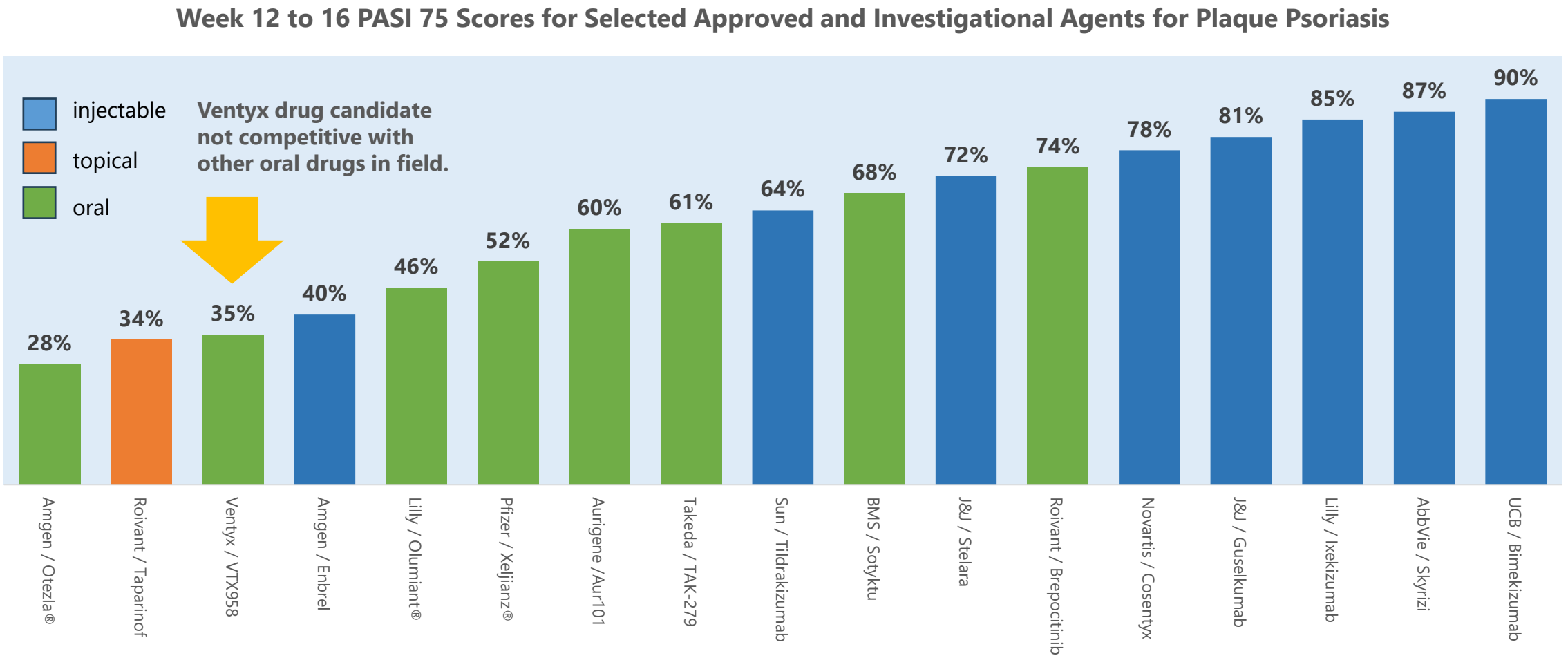
Primary and Secondary Endpoints at Week 16



Needed to dose BID testing to get to higher efficacy levels.

*p<0.05; **p<0.005; ***p<0.001.
P values from Cochran-Mantel-Haenszel test, using prior biologic treatment as a stratification factor.
PASI: Psoriasis Area and Severity Index; BID: twice daily; QD: once daily. Full analysis set with non-responder imputation. Source: Ventyx data on file.

PASI 75 Scores at 12 Weeks From Various Psoriasis Drugs

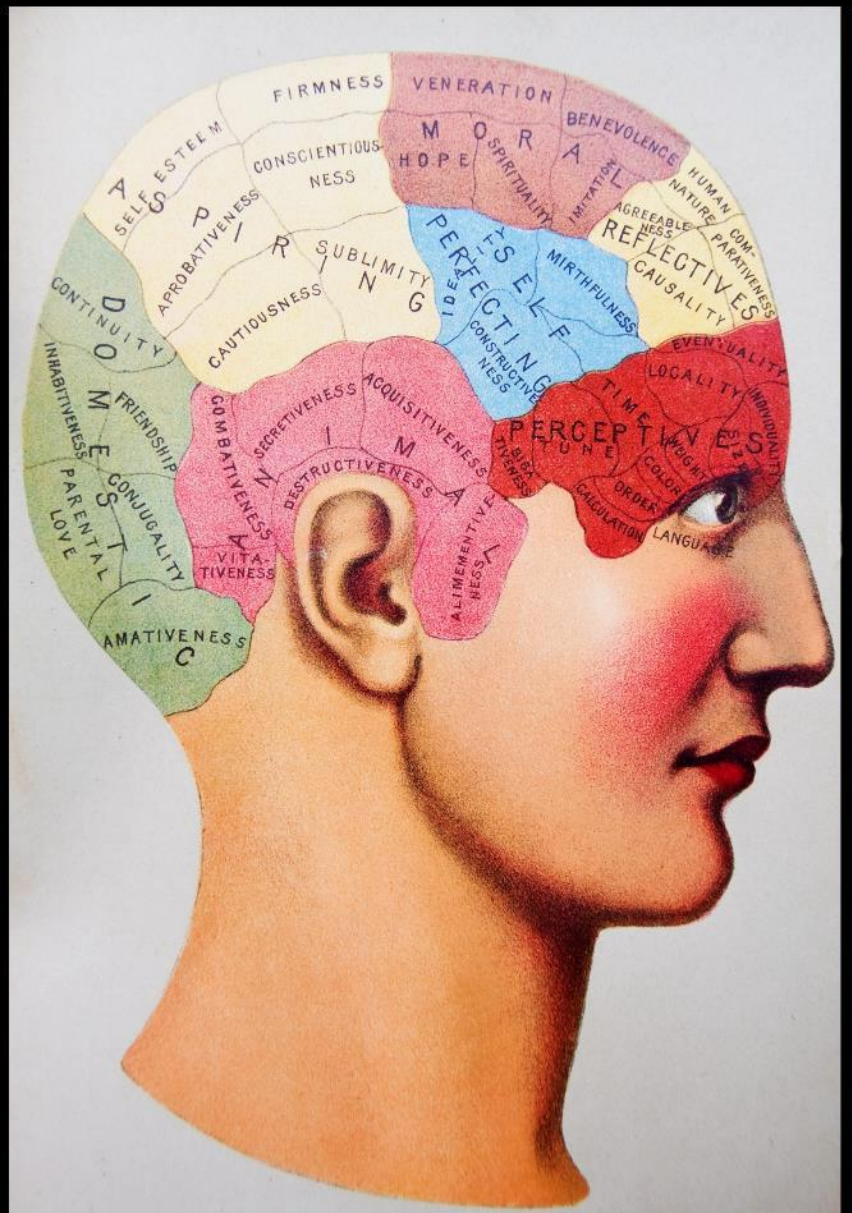


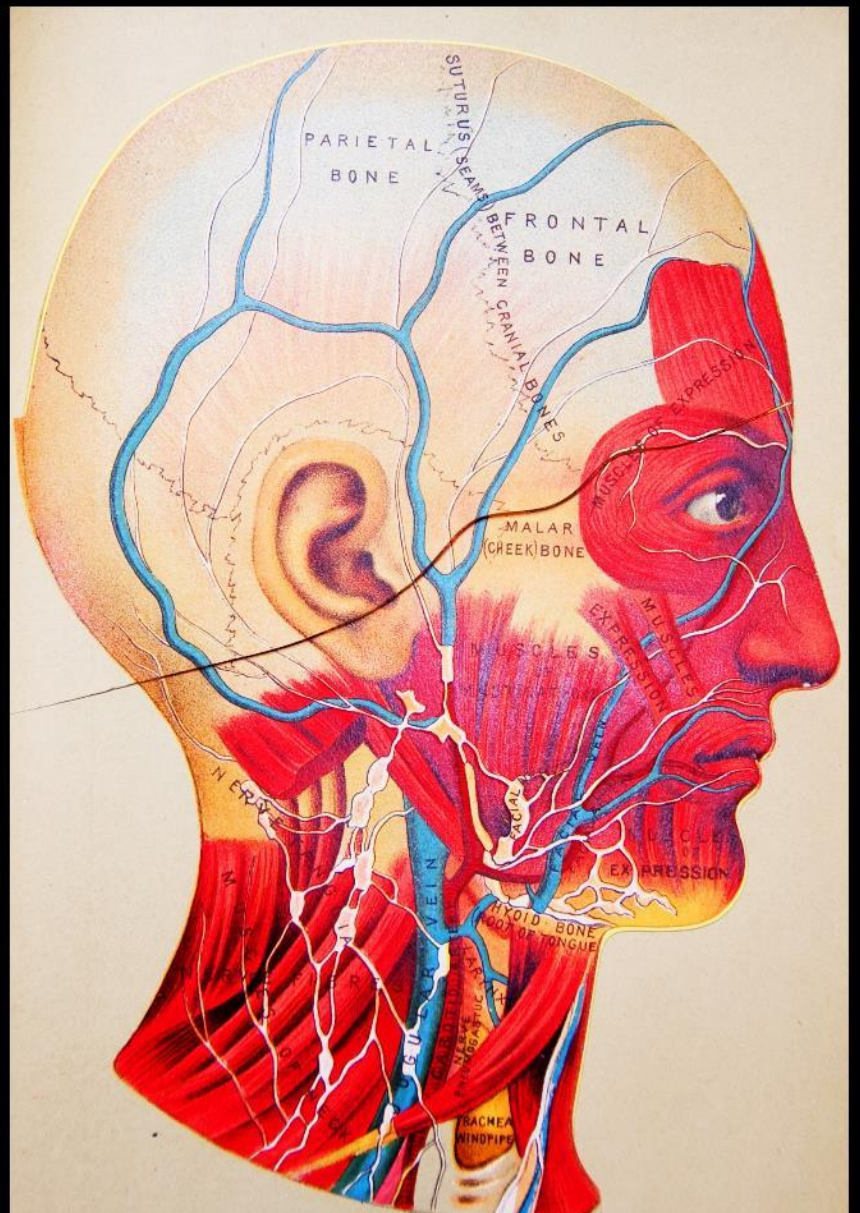
Note: Psoriasis is a chronic condition that can cause thick, scaly patches, or plaques, to form on the skin. The Psoriasis Area and Severity Index (PASI) score is a measurement of the discoloration, thickness, scaling, and coverage of these plaques. A doctor can use it to measure the severity and extent of psoriasis and observe the effectiveness of psoriasis treatments. A PASI 75 score is a binary outcome that is hit when the PASI score is reduced by 75% or more.

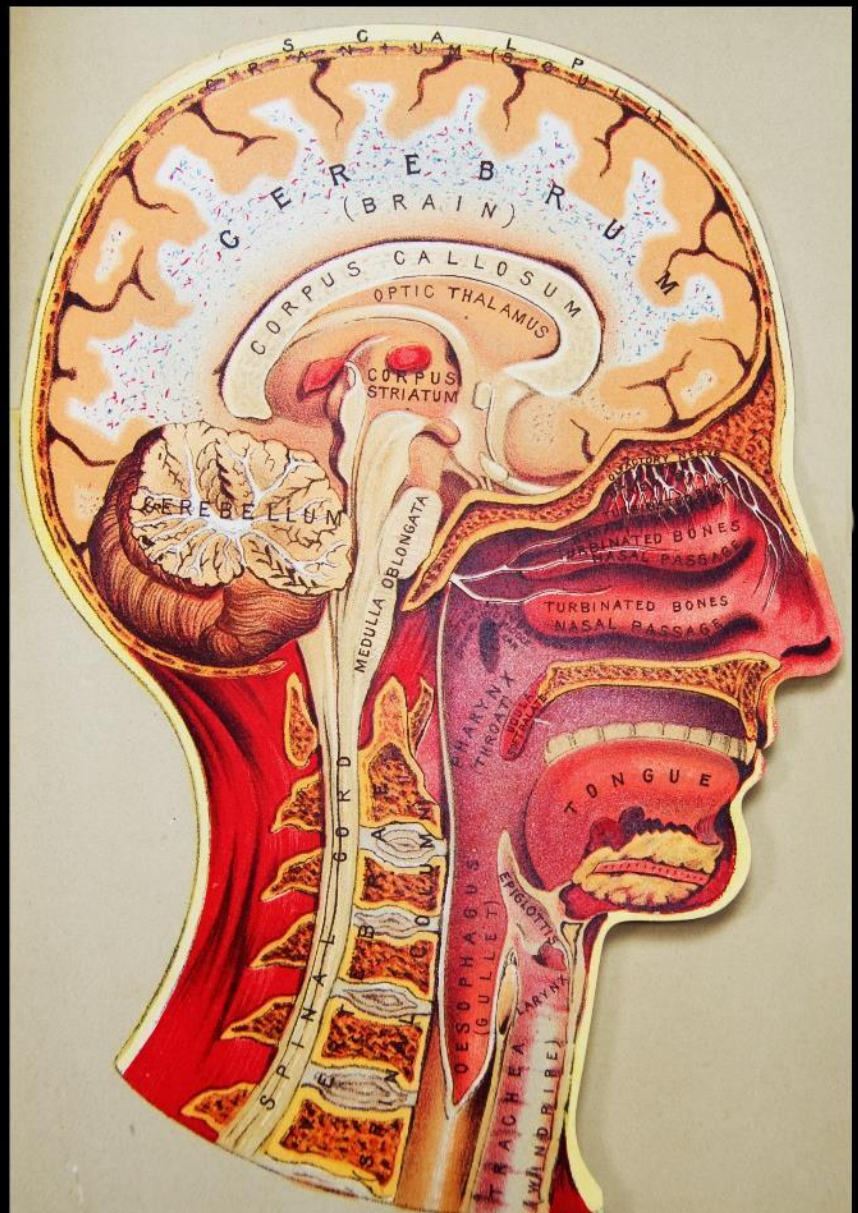
Source: Stifel research of press releases and articles with clinical data.

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

Science Updates







Drugs Like Tirzepatide with GIPR Agonism Appear to Achieve Weight Loss, in Part, Through a GABA Mechanism

nature metabolism

Letter

https://doi.org/10.1038/s42255-023-00931-7

Glucose-dependent insulinotropic polypeptide regulates body weight and food intake via GABAergic neurons in mice

Received: 15 July 2023

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Check for updates

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The development of single-molecule co-agonists for the glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) is considered a breakthrough in the treatment of obesity and type 2 diabetes. But although GIPR–GLP-1R co-agonism decreases body weight with superior efficacy relative to GLP-1R agonism alone in preclinical and clinical studies, the role of GIP in regulating energy metabolism remains enigmatic. Increasing evidence suggests that long-acting GIPR agonists act in the brain to decrease body weight through the inhibition of food intake; however, the mechanisms and neuronal populations through which GIP affects metabolism remain to be identified. Here, we report that long-acting GIPR agonists and GIPR–GLP-1R co-agonists decrease body weight and food intake via inhibitory GABAergic neurons. We show that acyl-GIP decreases body weight and food intake in male diet-induced obese wild-type mice, but not in mice with deletion of Gipr in Vgat(also known as Slc32a1)-expressing GABAergic neurons (Vgat-Gipr knockout). Whereas the GIPR–GLP-1R co-agonist MAR709 leads, in male diet-induced obese wild-type mice, to greater weight loss and further inhibition of food intake relative to a pharmacokinetically matched acyl-GLP-1 control, this superiority over GLP-1 vanishes in Vgat-Gipr knockout mice. Our data demonstrate that long-acting GIPR agonists crucially depend on GIPR signaling in inhibitory GABAergic neurons to decrease body weight and food intake.

Source: https://www.nature.com/articles/s42255-023-00931-7

Lower Sodium Intake Quickly Reduces Hypertension

November 11, 2023

Effect of Dietary Sodium on Blood Pressure

A Crossover Trial

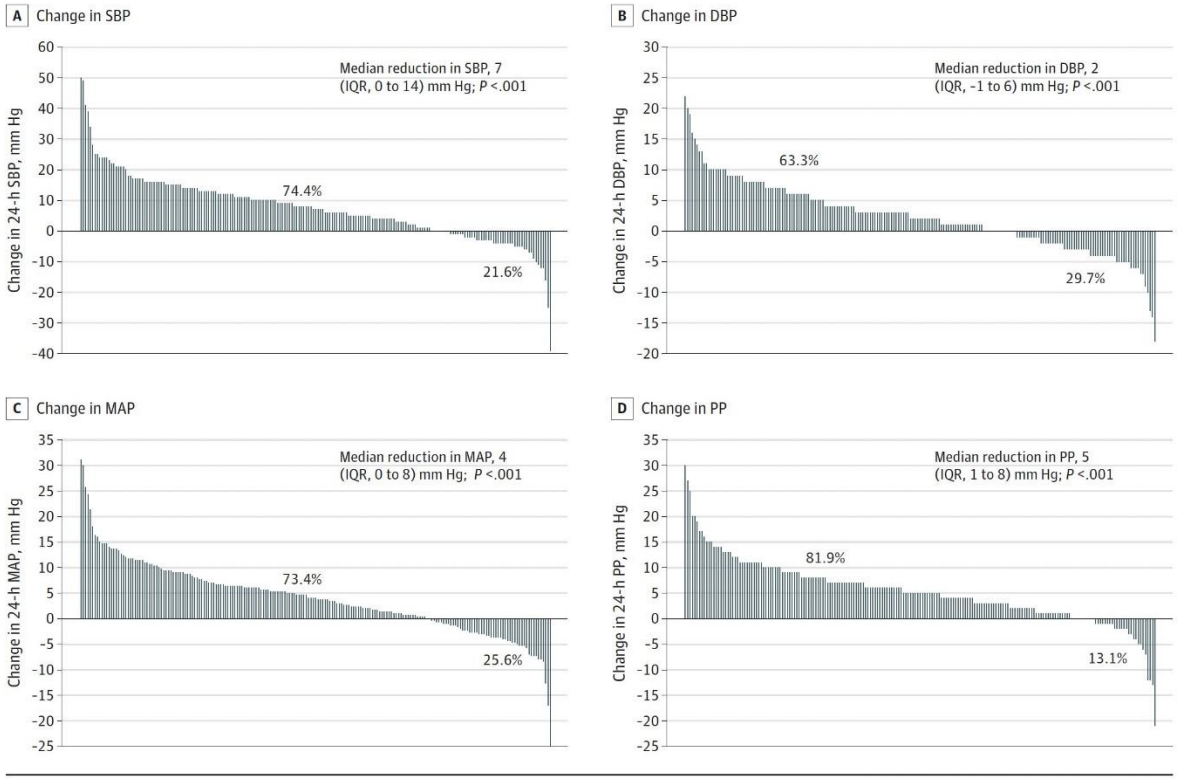
Deepak K. Gupta, MD, MSCI[1,2]; Cora E. Lewis, MD, MSPH[3]; Krista A. Varady, PhD[4]; et al

» Author Affiliations | Article Information

JAMA. Published online November 11, 2023. doi:10.1001/jama.2023.23651

Lowering salt (one teaspoon) in the diet among middle-aged and older adults was as good an effect for reducing BP as a first-line anti-hypertensive drug, independent of severity of hypertension or meds, in ~75% of people, from a randomized trial

Figure 2. Distributions of Within-Individual 24-Hour Ambulatory BP Response to Dietary Sodium Intake, Calculated From High-Sodium Diet Minus Low-Sodium Diet

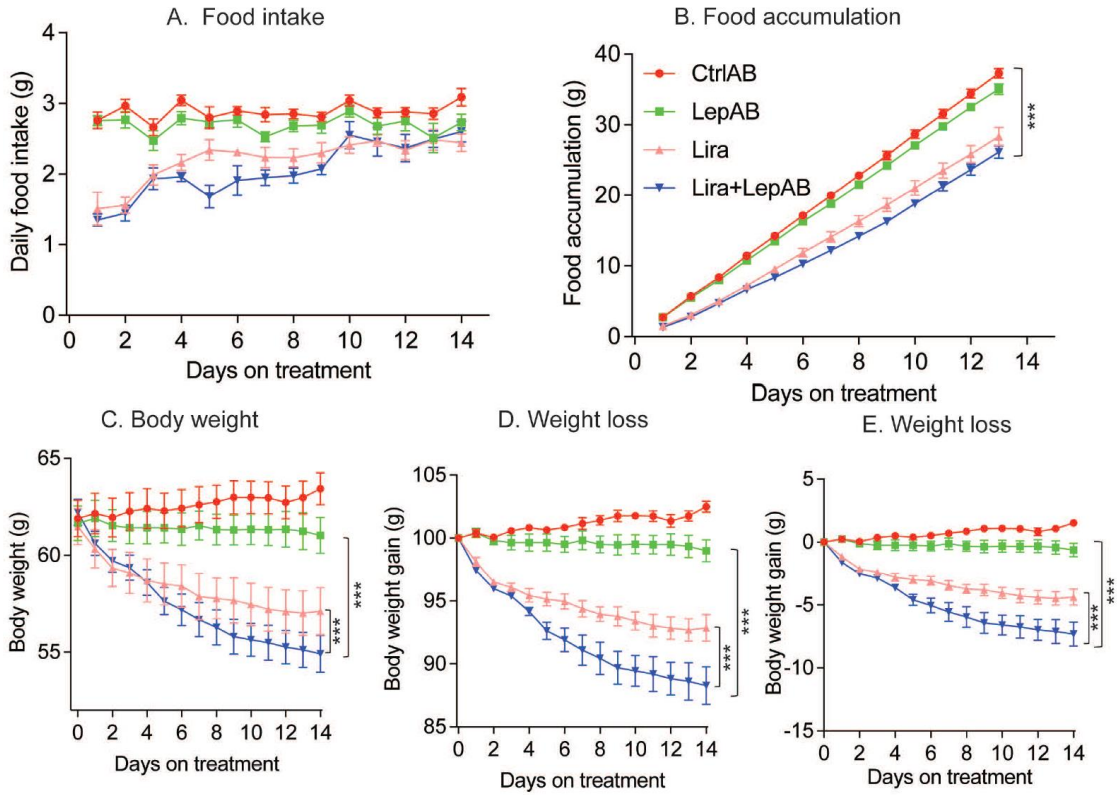


Source: https://jamanetwork.com/journals/jama/fullarticle/2811931

Leptin Reduction as a Required Component for Weight Loss

Zhao S, Li N, Xiong W, Li G, He S, Zhang Z, Zhu Q, Jiang N, Ikejiofor C, Zhu Y, Wang MY, Han X, Zhang N, Herrera-Solis C, Kusminski C, An Z, Elmquist JK, Scherer PE. Leptin Reduction as a Required Component for Weight Loss. *Diabetes,* 2023 Nov 7:db230571.

Partial leptin reduction can induce significant weight loss, while weight loss contributes to partial leptin reduction. The cause-and-effect relationship between leptin reduction and weight loss remains to be further elucidated. Here, we show that FGF21 and the GLP1R agonist liraglutide rapidly induce a reduction in leptin. This leptin reduction contributes to the beneficial effects of GLP1R agonism in metabolic health, as transgenically maintaining leptin levels during treatment partially curtails the beneficial effects seen with these agonists. Moreover, a higher degree of leptin reduction during treatment, induced by including a leptin neutralizing antibody with either FGF21 or liraglutide, synergistically induces greater weight loss and better glucose tolerance in diet-induced obese mice. Furthermore, upon cessation of either liraglutide or FGF21 treatment, the expected immediate weight regain is observed, associated with a rapid increase in circulating leptin levels. Prevention of this leptin surge with leptin neutralizing antibodies slows down weight gain and preserves a better glucose tolerance. Mechanistically, a significant reduction in leptin induces a higher degree of leptin sensitivity in hypothalamic neurons. Our observations support a model that postulates that a reduction of leptin levels is a necessary prerequisite for substantial weight loss and partial leptin reduction is a viable strategy to treat obesity and its associated insulin resistance.



Source: https://diabetesjournals.org/diabetes/article-abstract/doi/10.2337/db23-0571/153835/Leptin-Reduction-as-a-Required-Component-for

nature chemical biology

Article

https://doi.org/10.1038/s41589-023-01466-4

Checkpoint kinase 2 controls insulin secretion and glucose homeostasis

Received: 29 November 2021

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Check for updates

Angie Chi Nok Chong[1,2], J. Jeya Vandana[1,2,3], Ginnie Jeng[4], Ge Li[5,12], Zihe Meng[1,2], Xiaohua Duan[1,2], Tuo Zhang[6], Yunping Qiu[7], Raimon Duran-Struuck[8], Kimberly Coker[8], Wei Wang[9], Yanjing Li[9], Zaw Min[9], Xi Zuo[9], Neranjan de Silva[1], Zhengming Chen[10], Ali Naji[8], Mingming Hao[11], Chengyang Liu[9,13] ✉ & Shuibing Chen[1,2,13] ✉

After the discovery of insulin, a century ago, extensive work has been done to unravel the molecular network regulating insulin secretion. Here we performed a chemical screen and identified AZD7762, a compound that potentiates glucose-stimulated insulin secretion (GSIS) of a human β cell line, healthy and type 2 diabetic (T2D) human islets and primary cynomolgus macaque islets. In vivo studies in diabetic mouse models and cynomolgus macaques demonstrated that AZD7762 enhances GSIS and improves glucose tolerance. Furthermore, genetic manipulation confirmed that ablation of *CHEK2* in human β cells results in increased insulin secretion. Consistently, high-fat-diet-fed *Chk2*$^{-/-}$ mice show elevated insulin secretion and improved glucose clearance. Finally, untargeted metabolic profiling demonstrated the key role of the CHEK2–PP2A–PLK1–G6PD–PPP pathway in insulin secretion. This study successfully identifies a previously unknown insulin secretion regulating pathway that is conserved across rodents, cynomolgus macaques and human β cells in both healthy and T2D conditions.

Identification of Circulating Proteins Associated with General Cognitive Function Among Middle-Aged and Older Adults

Tin A, et.al., *Commun Biol*. 2023 Nov 3;6(1):1117.

Identifying circulating proteins associated with cognitive function may point to biomarkers and molecular process of cognitive impairment. Few studies have investigated the association between circulating proteins and cognitive function. We identify 246 protein measures quantified by the SomaScan assay as associated with cognitive function ($p < 4.9E-5$, n up to 7289). Of these, 45 were replicated using SomaScan data, and three were replicated using Olink data at Bonferroni-corrected significance. Enrichment analysis linked the proteins associated with general cognitive function to cell signaling pathways and synapse architecture. **Mendelian randomization analysis implicated higher levels of NECTIN2, a protein mediating viral entry into neuronal cells, with higher Alzheimer's disease (AD) risk ($p = 2.5E-26$).** Levels of 14 other protein measures were implicated as consequences of AD susceptibility ($p < 2.0E-4$).

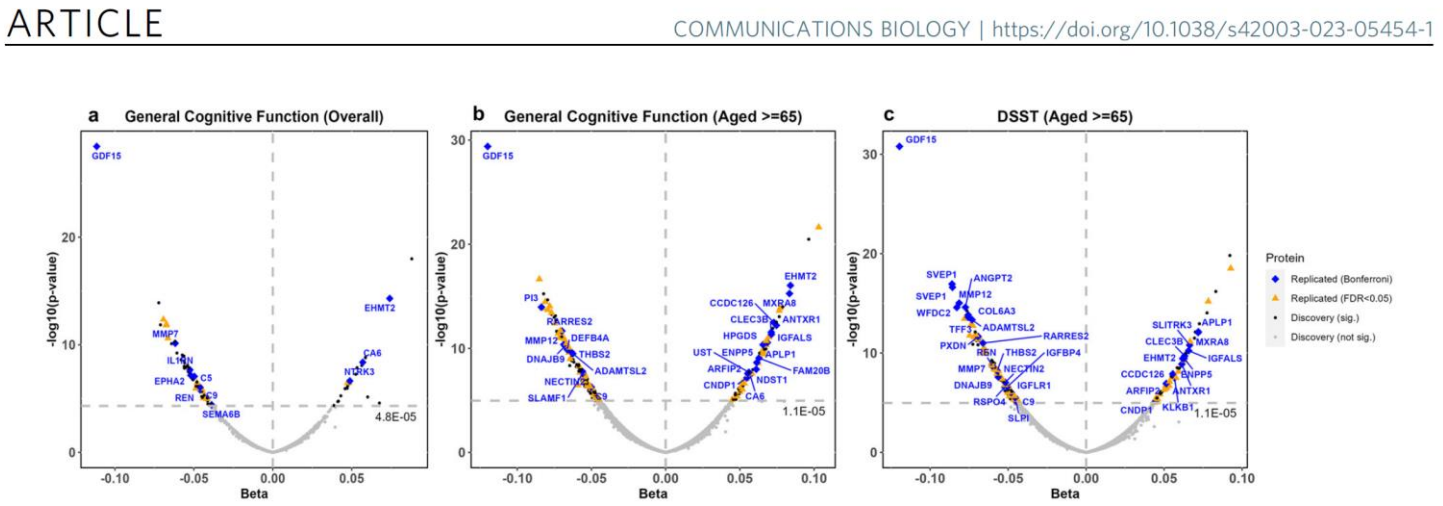

Fig. 2 Volcano plots showing the beta coefficients and *p*-values from the discovery meta-analyses with colors indicating whether a protein was replicated. The three discovery analyses were for general cognitive function among aged ≥25 (**a**) and aged ≥65 (**b**), and performance on the Digit Symbol Substitution Test (**c**).

Source: https://www.nature.com/articles/s42003-023-05454-1

Meet BATF3: Regulator of T-Cell Exhaustion

Transcriptional and epigenetic regulators of human CD8$^+$ T cell function identified through orthogonal CRISPR screens

Nature Genetics

Received: 18 July 2023

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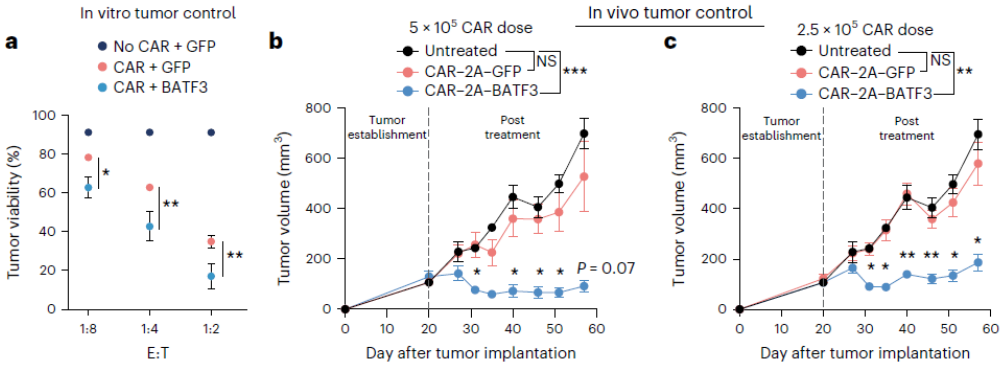
Published online: 09 November 2023

Check for updates

Sean R. McCutcheon[1,2], Adam M. Swartz[3], Michael C. Brown[4], Alejandro Barrera[2,5], Christian McRoberts Amador[2,6], Keith Siklenka[2,5], Lucas Humayun[1], Maria A. ter Weele[1,2], James M. Isaacs[7], Timothy E. Reddy[1,2,5], Andrew S. Allen[2,5], Smita K. Nair[3,7,8], Scott J. Antonia[7] & Charles A. Gersbach[1,2,3]

Clinical response to adoptive T cell therapies is associated with the transcriptional and epigenetic state of the cell product. Thus, discovery of regulators of T cell gene networks and their corresponding phenotypes has potential to improve T cell therapies. Here we developed pooled, epigenetic CRISPR screening approaches to systematically profile the effects of activating or repressing 120 transcriptional and epigenetic regulators on human CD8+ T cell state. We found that BATF3 overexpression promoted specific features of memory T cells and attenuated gene programs associated with cytotoxicity, regulatory T cell function, and exhaustion. Upon chronic antigen stimulation, BATF3 overexpression countered phenotypic and epigenetic signatures of T cell exhaustion. Moreover, BATF3 enhanced the potency of CAR T cells in both in vitro and in vivo tumor models and programmed a transcriptional profile that correlates with positive clinical response to adoptive T cell therapy. Finally, we performed CRISPR knockout screens that defined cofactors and downstream mediators of the BATF3 gene network.



BATF3 OE enhances CAR T cell potency. a, Tumor viability after coculture at specified E:T ratios (n = 3 donors). A two-way ANOVA with Dunnett's post hoc test compared tumor viability at each E:T ratio: 1:8 (Padj = 0.0243), 1:4 (Padj = 0.0042) and 1:2 (Padj = 0.0099). b,c, Tumor volumes of untreated (n = 5) and treated mice with 5 × 105 (n = 1 donor, 5 mice per treatment) (b) or 2.5 × 105 CAR T cells (n = 1 donor, 4 mice per treatment) (c) with or without BATF3 OE. Two-way ANOVA with Tukey's post hoc tests compared tumor volumes at each time point across treatments. Tumor volumes were never different between untreated and control CAR groups. Asterisks indicate significant differences between control and BATF3 OE CAR T cells.

Source: https://www.nature.com/articles/s41588-023-01554-0

Regeneron Paper: Anterior Uveitis and ERAP1

nature communications

Article

https://doi.org/10.1038/s41467-023-43036-1

A large meta-analysis identifies genes associated with anterior uveitis

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Check for updates

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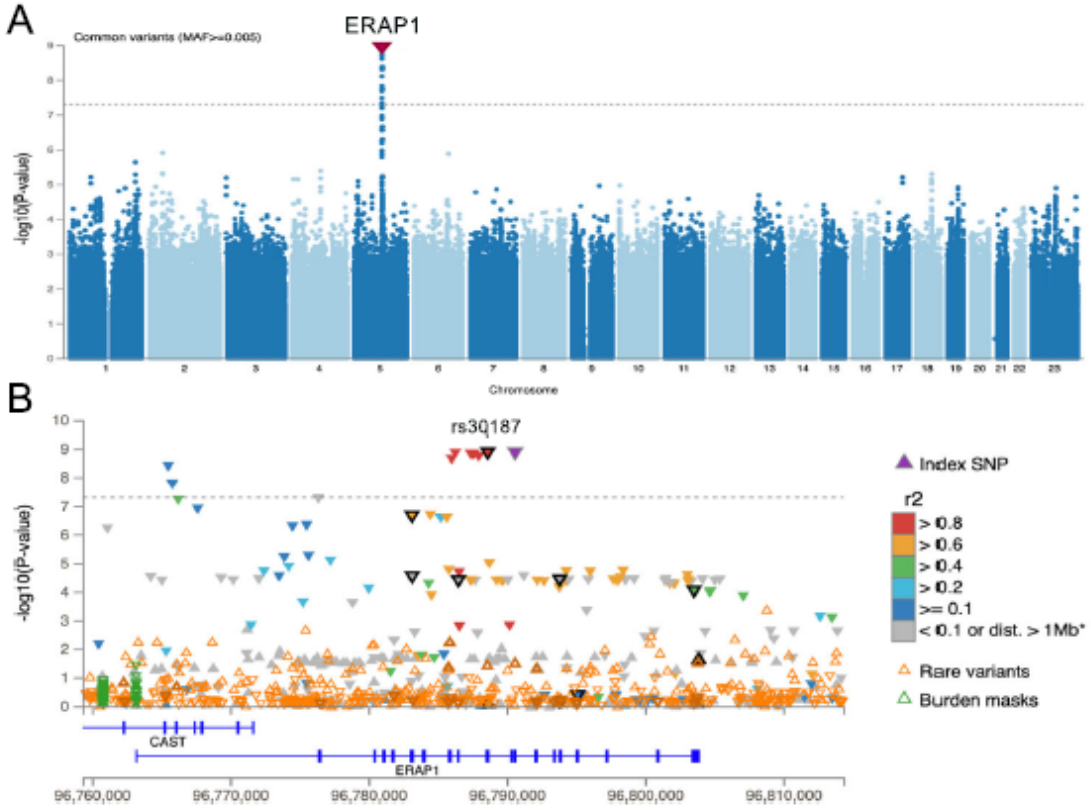
Anterior Uveitis (AU) is the inflammation of the anterior part of the eye, the iris and ciliary body and is strongly associated with HLA-B*27. We report AU exome sequencing results from eight independent cohorts consisting of 3,850 cases and 916,549 controls. We identify common genome-wide significant loci in HLA-B (OR = 3.37, p = 1.03e-196) and ERAP1 (OR = 0.86, p = 1.1e-08), and find IPMK (OR = 9.4, p = 4.42e-09) and IDO2 (OR = 3.61, p = 6.16e-08) as genome-wide significant genes based on the burden of rare coding variants. Dividing the cohort into HLA-B*27 positive and negative individuals, we find ERAP1 haplotype is strongly protective only for B*27-positive AU (OR = 0.73, p = 5.2e-10). Investigation of B*27-negative AU identifies a common signal near HLA-DPB1 (rs3117230, OR = 1.26, p = 2.7e-08), risk genes IPMK and IDO2, and several additional candidate risk genes, including ADGFR5, STXBP2, and ACHE. Taken together, we decipher the genetics underlying B*27-positive and -negative AU and identify rare and common genetic signals for both subtypes of disease.



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Study	Cases	Controls	AAF	OR	Pval
UKB	63 | 225 | 136	4,057 | 15,834 | 15,573	0.66	0.74	1.60e−05
GHS	29 | 104 | 55	1,465 | 5,536 | 5,480	0.66	0.78	1.00e−02
MAYO−CLINIC	11 | 38 | 25	1,141 | 4,444 | 4,317	0.66	0.76	1.20e−01
Colorado	11 | 23 | 13	432 | 1,678 | 1,588	0.65	0.70	3.90e−02
UPENN−PMBB	4 | 8 | 7	294 | 1,048 | 1,010	0.65	0.65	2.50e−01
UCLA	9 | 33 | 12	333 | 1,046 | 927	0.63	0.68	8.60e−02
SINAI	2 | 14 | 4	182 | 515 | 391	0.60	0.65	2.90e−01
MALMO	5 | 13 | 12	326 | 1,275 | 1,217	0.66	0.87	6.40e−01
Meta	**134 | 458 | 264**	**8,230 | 31,376 | 30,503**	**0.66**	**0.74**	**1.60e−09**

Source: https://www.nature.com/articles/s41467-023-43036-1

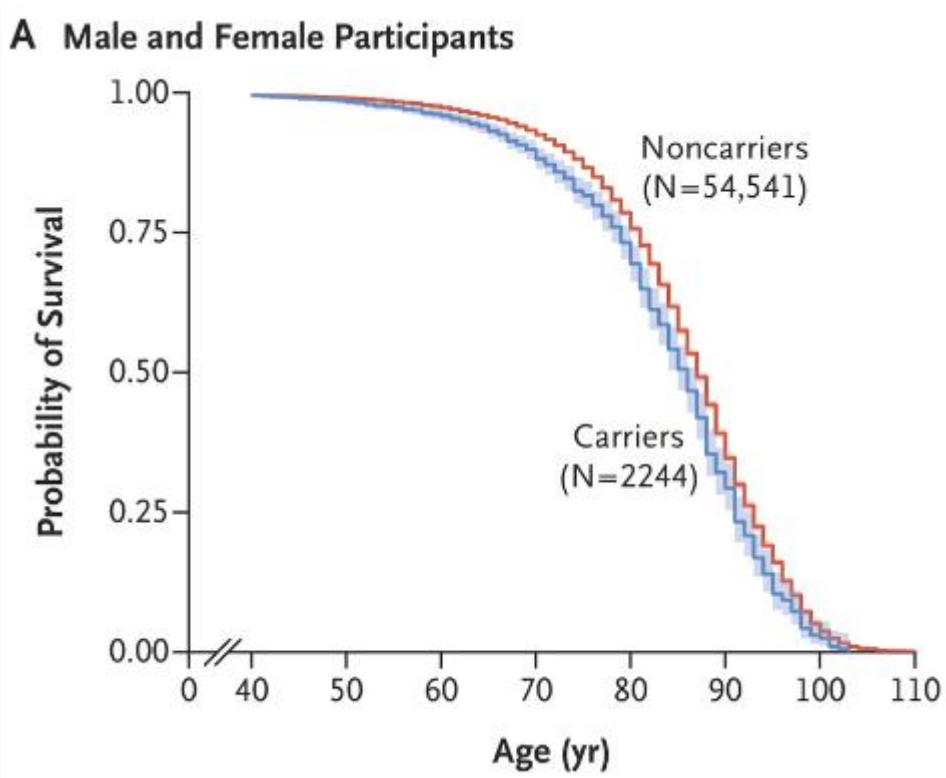
Is Population Genotyping Worthwhile?

November 9, 2023
N Engl J Med 2023; 389:1741-1752

Actionable Genotypes and Their Association with Life Span in Iceland

Brynjar O. Jensson, M.Sc., Gudny A. Arnadottir, M.Sc., Hildigunnur Katrinardottir, M.Sc., Run Fridriksdottir, M.Sc., Hannes Helgason, Ph.D., Asmundur Oddsson, Ph.D., Gardar Sveinbjornsson, M.Sc., Hannes P. Eggertsson, Ph.D., Gisli H. Halldorsson, M.Sc., Bjarni A. Atlason, B.A., Hakon Jonsson, Ph.D., Gudjon R. Oskarsson, Ph.D., et al.

Through manual curation of 4405 sequence variants in the ACMG SF v3.0 genes, we identified 235 actionable genotypes in 53 genes. Of the 57,933 participants, 2306 (4.0%) carried at least one actionable genotype. We found shorter median survival among persons carrying actionable genotypes than among noncarriers. Specifically, we found that carrying an actionable genotype in a cancer gene was associated with survival that was 3 years shorter than that among noncarriers, with causes of death among carriers attributed primarily to cancer-related conditions. Furthermore, we found evidence of association between carrying an actionable genotype in certain genes in the cardiovascular disease group and a reduced life span.

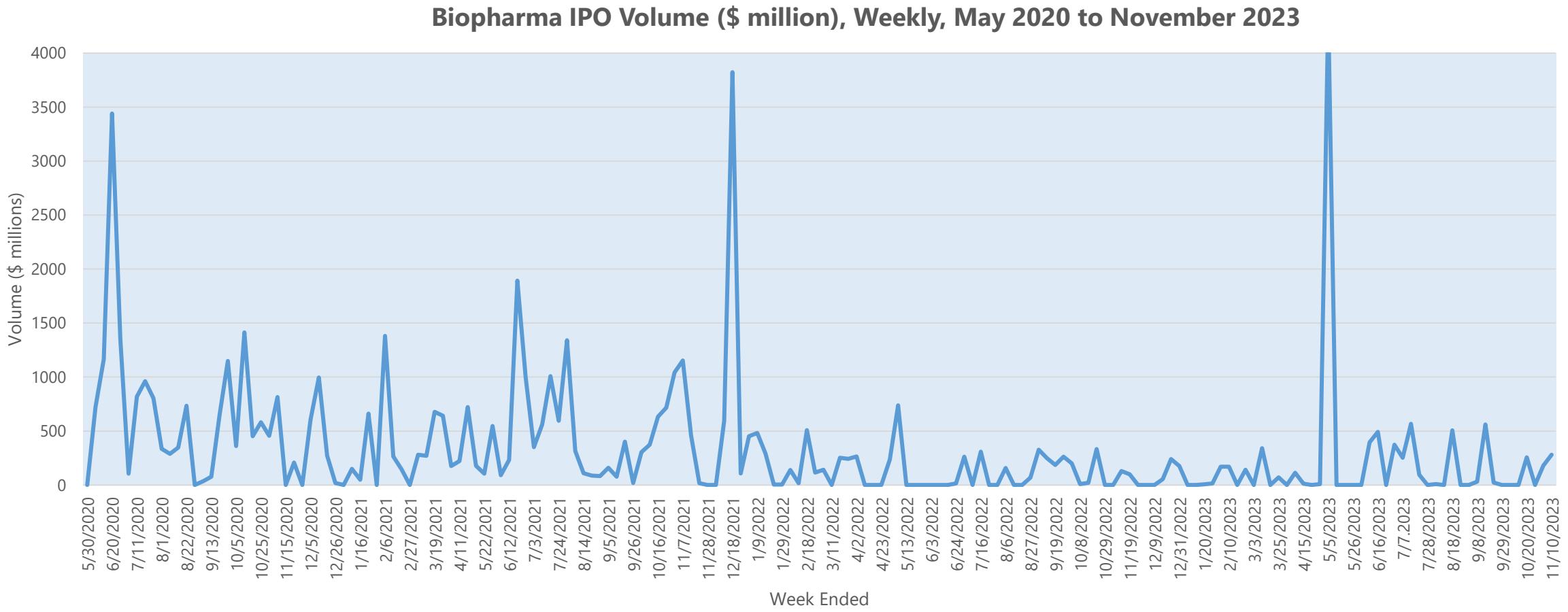


Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2300792

Capital Markets Update

IPO Market Saw One Transaction Last Week

Last week saw CARGO Therapeutics go public amidst very difficult market conditions. The deal closed the week below offer despite strong insider participation.



Source: Data from CapitalIQ and Stifel research.

CARGO Therapeutics Prices $281 Million IPO

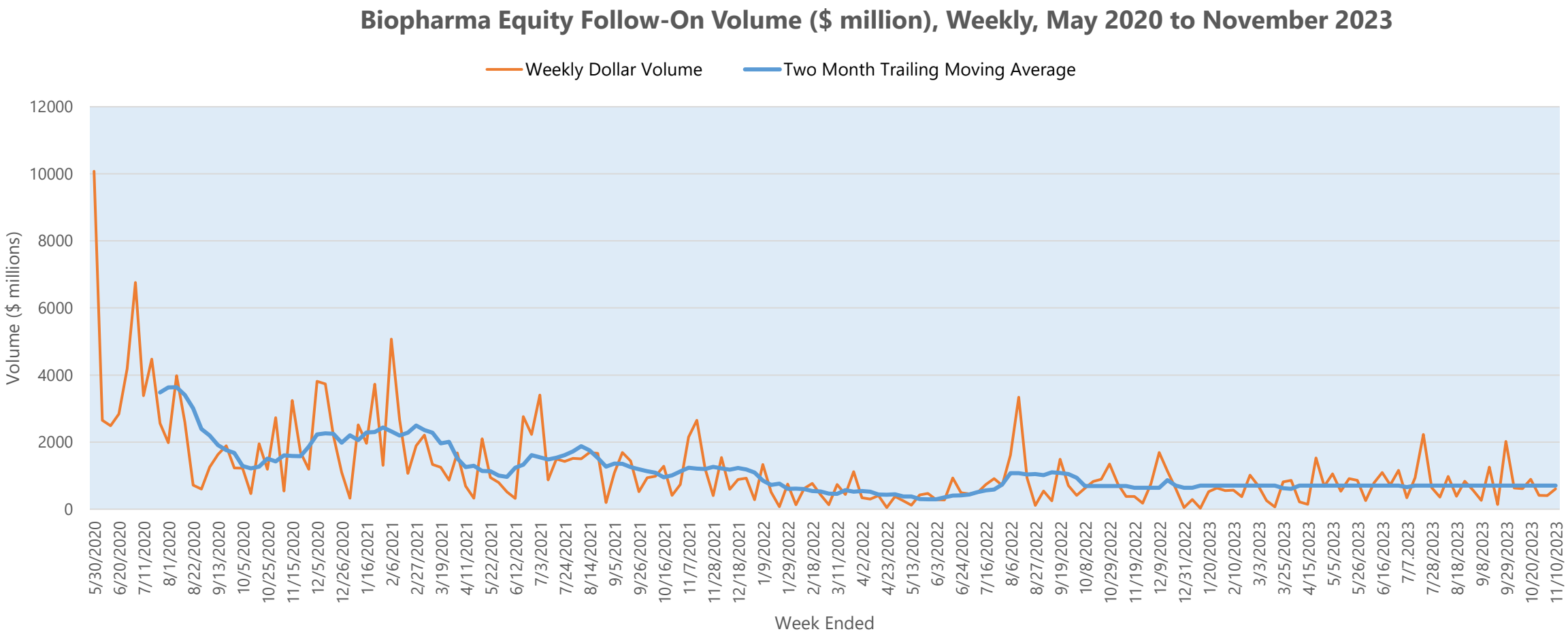
SAN MATEO, Calif., Nov. 09, 2023 (GLOBE NEWSWIRE) -- CARGO Therapeutics, Inc. ("CARGO"), a clinical-stage biotechnology company positioned to advance next generation, potentially curative cell therapies for cancer patients, today announced the pricing of its initial public offering of 18,750,000 shares of its common stock at a public offering price of $15.00 per share. All of the shares of common stock are being offered by CARGO. The gross proceeds from the offering, before deducting underwriting discounts and commissions and other offering expenses payable by CARGO, are expected to be approximately $281.3 million. In addition, CARGO has granted the underwriters a 30-day option to purchase up to 2,812,500 additional shares of common stock at the initial public offering price, less the underwriting discounts and commissions. CARGO's common stock is expected to begin trading on the Nasdaq Global Select Market on November 10, 2023 under the ticker symbol "CRGX." The offering is expected to close on November 14, 2023, subject to the satisfaction of customary closing conditions.

CARGO is developing next-generation transformational CAR T-cell therapies with the mission of outsmarting cancer to deliver more cures for patients.

Source: https://investors.cargo-tx.com/news-releases/news-release-details/cargo-therapeutics-announces-pricing-initial-public-offering

Last Week Was Active for Follow-On Offerings

Last week saw $640 million in follow-on equity volume. The largest transactions were raises by Celldex and Alpine Immune. The market remains highly catalyst driven.



Source: Data from CapitalIQ and Stifel research.

Celldex Prices $200 Million Follow-on Offering

HAMPTON, N.J., Nov. 07, 2023 (GLOBE NEWSWIRE) -- Celldex Therapeutics, Inc. ("Celldex" or the "Company") (Nasdaq: CLDX) today announced the pricing of an underwritten public offering of 7,425,000 shares of its common stock at a public offering price of $27.00 per share. In connection with the offering, Celldex has granted the underwriters a 30-day option to purchase up to an additional 1,113,750 shares of common stock at the public offering price, less underwriting discounts and commissions.

The Company expects to receive gross proceeds from the offering, excluding the exercise of the underwriters' option, if any, of approximately $200.5 million, excluding underwriting discounts and commissions and other offering-related expenses.

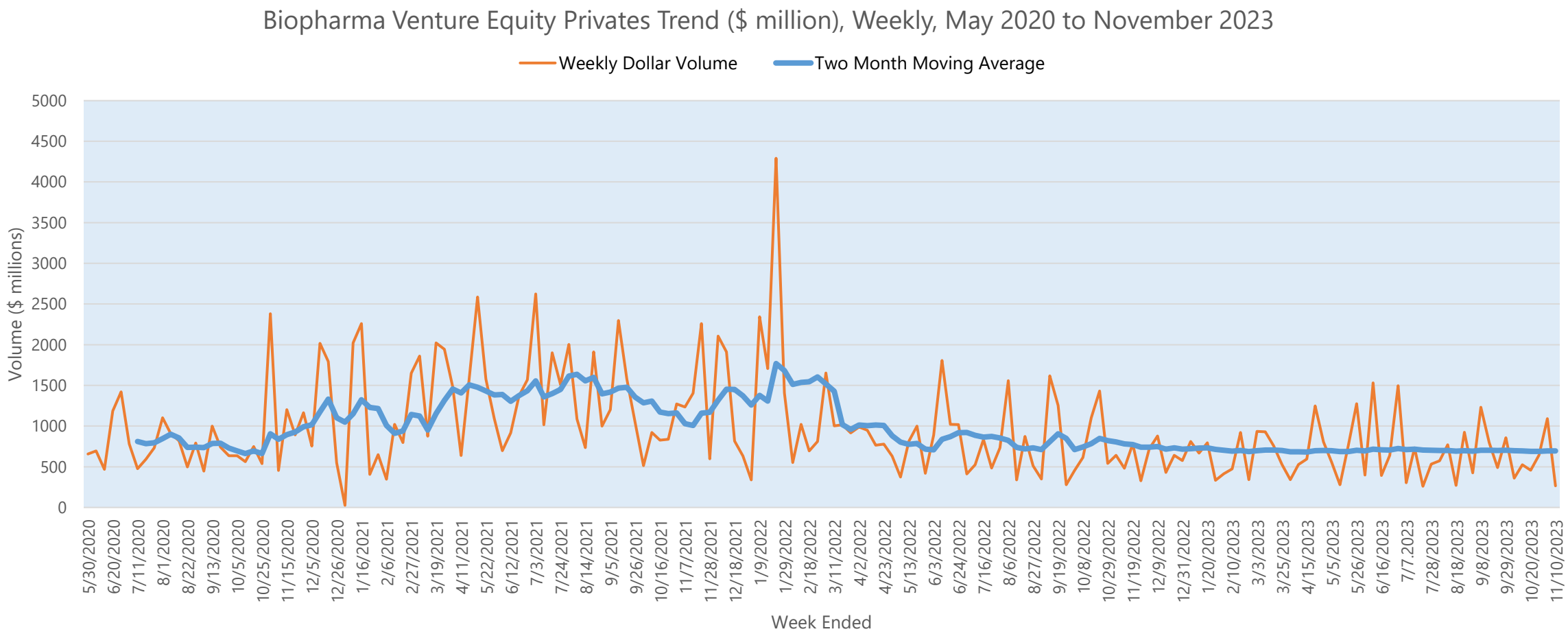
Celldex intends to use the net proceeds from the offering to continue clinical and preclinical development of its product candidates, including current and future development of barzolvolimab, growing its bispecific antibody platform and clinical candidates, funding ongoing efforts to develop additional clinical pipeline products and for general corporate purposes.

The offering is expected to close on or about November 10, 2023, subject to customary closing conditions.

Source: https://ir.celldex.com/news-releases/news-release-details/celldex-therapeutics-announces-pricing-public-offering-common

Venture Equity Market Moribund Last Week

Last week saw fifteen companies raise $267 million in the venture equity market. This was the second slowest week of the year.



Source: Data from CapitalIQ, Crunchbase.

An Obesity Drug Biotech Gets Buy-in From Eli Lilly, Venture Firms

Gwendolyn Wu, *Biopharma Dive*, November 7, 2023

Obesity affects a large swathe of the U.S. adult population and the many health issues — particularly the metabolic disorders — that can result from excess weight have made it an emerging research priority.

The success of GLP-1 drugs in managing diabetes and weight loss has also fueled billions of dollars in sales for Lilly, which makes Mounjaro, and Novo Nordisk, the maker of Ozempic and Wegovy.

While those medicines are potent, drugmakers still see room for improvement. Companies like OrsoBio have stepped in with plans for complementary therapies, for instance.

OrsoBio's lead program, dubbed TLC-3595, is already in a Phase 2 study for diabetes. And the startup has now drawn the interest of both seasoned biotech investors and Lilly with a pipeline of three other drugs that work in different ways.

According to OrsoBio CEO Mani Subramanian, the investment from the pharmaceutical company reinforced a "commitment to furthering new approaches."

"They're quite interested in all four mechanisms of action, but particularly interested in the protonophore program," Subramanian said, referring to one of its obesity drugs that targets the liver.

Source: https://www.biopharmadive.com/news/orsobio-series-a-eli-lilly-funding-obesity-drugs/698908/

Biotech Companies Tap Saudi Arabia for Venture Funding

Brian Gormley, *Wall Street Journal*, November 10, 2023

Some biotechnology startups are raising capital from Saudi Arabia as U.S. venture funding retreats and Middle East countries seek to boost their life-sciences industries.

Chicago-based Flashpoint Therapeutics recently raised seed financing led by Beta Lab, a new venture firm based in Riyadh, and biomedical startups including Insilico Medicine have secured funding from Prosperity7 Ventures, the venture fund of Aramco Ventures, a subsidiary of Saudi Arabia's national oil company.

Saudi Arabia, whose national oil company posted record profits in 2022, seeks to diversify its economy. It is well-positioned to establish a globally competitive biotech hub, said a report by Strategy&, a part of the PricewaterhouseCoopers network. The report cited developments such as the streamlining of regulatory frameworks for clinical trials, testing and bioethics.

Other Middle Eastern countries such as the United Arab Emirates are making similar efforts in biotech. "The region's become much more relevant within the biotech ecosystem," said Ali Siam, chief business officer of Rubedo Life Sciences, a longevity-focused biotech startup in Sunnyvale, Calif., that participated in a February longevity conference in Saudi Arabia.

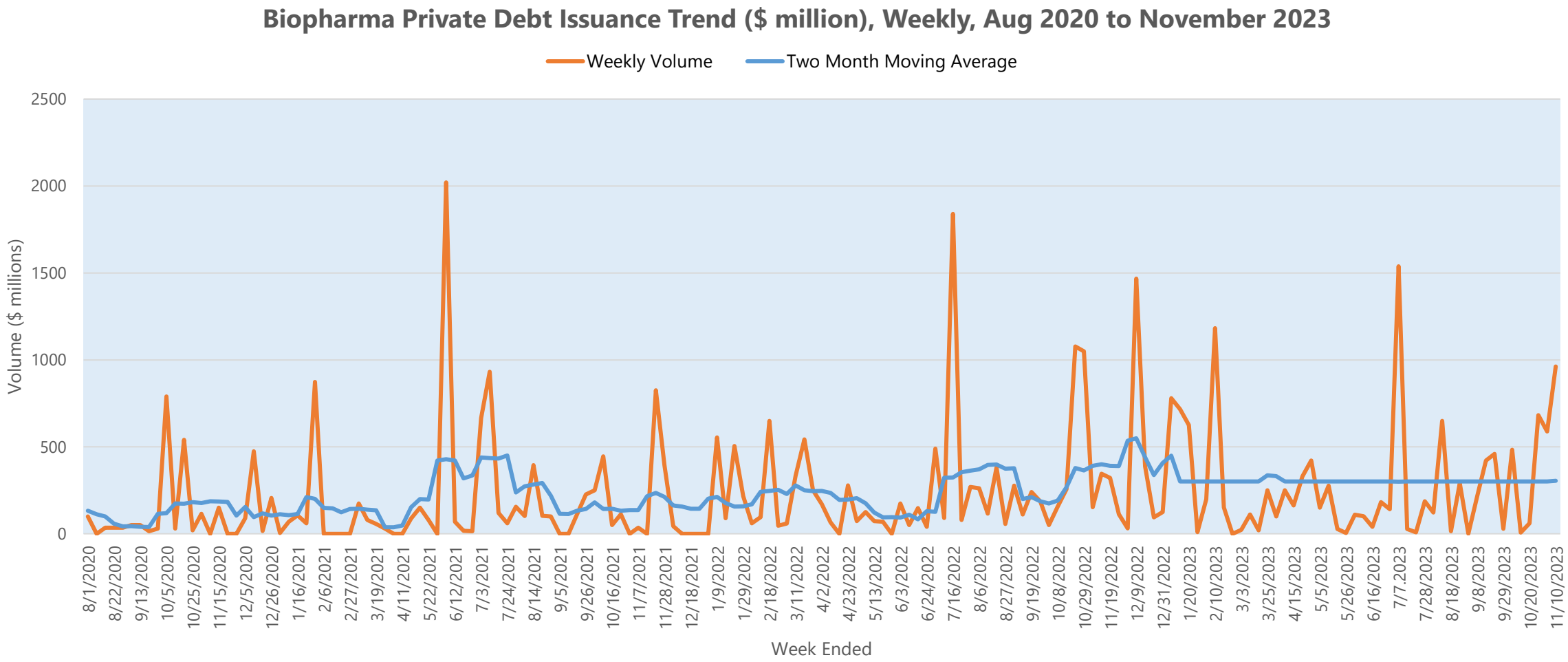
Saudi Arabian investors move quickly when they see opportunity, said Chad Mirkin, director of the International Institute for Nanotechnology at Northwestern University. Mirkin visited Riyadh in April to accept the King Faisal Prize, launched by the philanthropic King Faisal Foundation to recognize achievement in Islamic studies, science, medicine and other disciplines. While there, he said he toured universities and met with officials including the minister of investment and minister of communications and information technology.

He said those meetings led within six months to investments from Beta Lab in two companies founded around technology from his lab, Flashpoint Therapeutics, and 3-D printing company Azul 3D.

Source: https://www.wsj.com/articles/biotech-companies-tap-saudi-arabia-for-venture-funding-f09c0a88

Weekly Global Biopharma Private Debt Placements

We saw six deals in the private debt market last week with $962 million raised. It was the third most active week of the year.



Source: Data from CapitalIQ, Crunchbase.

Xencor Sells Portion of Royalties and Milestones from to OMERS Life Sciences for $215 Million

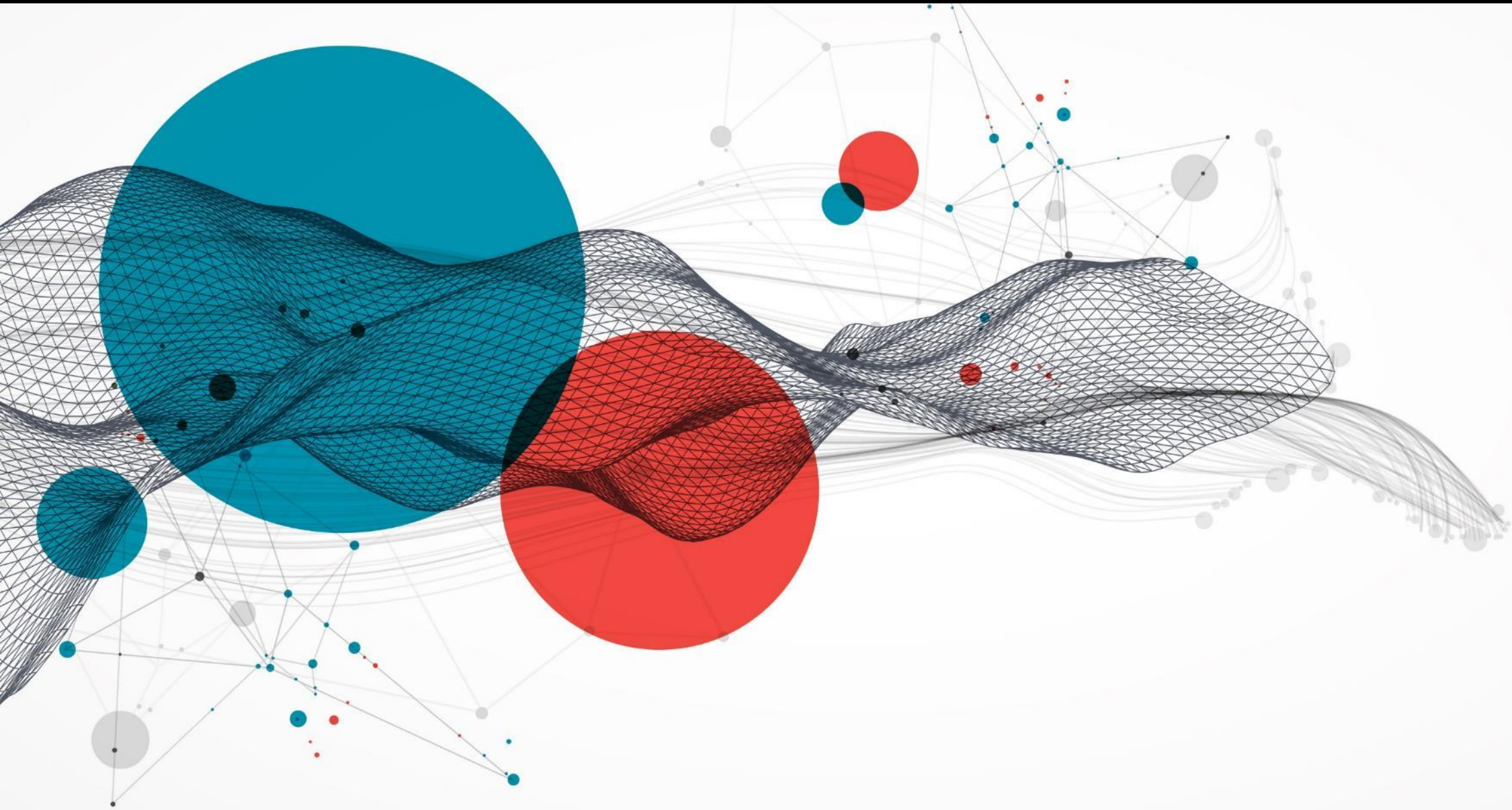
PASADENA, Calif.--(BUSINESS WIRE)--Nov. 7, 2023-- Xencor, Inc. (NASDAQ:XNCR), a clinical-stage biopharmaceutical company developing engineered antibodies and cytokines for the treatment of cancer and autoimmune diseases, today announced the sale of portions of financial interests from Alexion Pharmaceuticals, Inc., on sales of Ultomiris® (ravulizumab-cwvz) and from MorphoSys AG on sales of Monjuvi® (U.S.)/Minjuvi® (ex-U.S.) (tafasitamab-cxix) to OMERS, one of Canada's largest defined benefit pension plans.

Under the agreements, Xencor has received a $215 million payment from OMERS. OMERS has acquired royalties due to Xencor on global Ultomiris sales from July 1, 2023 onward, with annual caps beginning in 2026, and the majority of a milestone payment earned this year. Xencor will also be eligible for a new Ultomiris sales-based milestone payment from OMERS. OMERS has also acquired royalties on global Monjuvi sales from July 1, 2023 until OMERS has received 1.3 times the value of the Monjuvi purchase price.

"Xencor's modular XmAb® Fc domains and technologies are the foundation that enables our diversified approach to building value. Our platforms have been fundamental to the creation of three XmAb-based medicines marketed by partners, generating royalty income that drives further innovations in protein engineering and supports the advancement of our internal pipeline," said Bassil Dahiyat, Ph.D., president and chief executive officer at Xencor. "A strengthened financial position offers us additional flexibility to execute on our internal clinical development programs with the greatest potential for success, and importantly, we are retaining potential economic upside from the sales performance of Ultomiris and Monjuvi/Minjuvi."

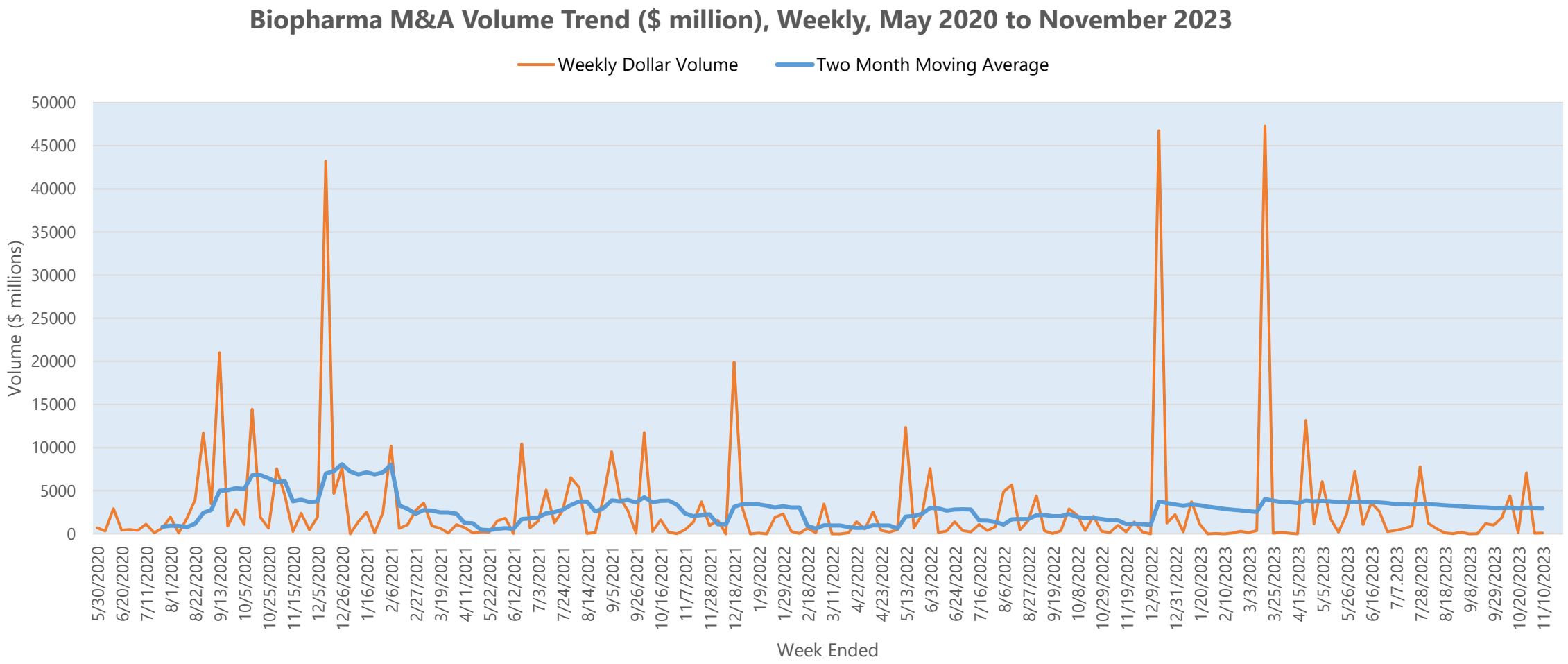
Source: https://investors.xencor.com/news-releases/news-release-details/xencor-sells-portion-royalties-and-milestones-ultomirisr-and

Deals Environment Update



M&A Market Quiet Last Week

Last week saw BioNTech acquire Aexerna. Newtyn Management offered to acquire Sensei BioTherapeutics for $32 million. Eris entered into an agreement to buy Biocon's formulation business in dermatology and nephrology in India for $44 million.



Source: S&P, CapitalIQ

Sensei Rejects Hostile Takeover Offer

8-K Filing, November 6, 2023

On November 6, 2023, Sensei Biotherapeutics, Inc. (the "Company") confirmed that on October 25, 2023 it received an unsolicited proposal from Newtyn Management, LLC ("Newtyn") to acquire all of the Company's outstanding shares of common stock at a price of $1.00 per share in cash.

The Company's Board of Directors ("Board") reviewed Newtyn's proposal and determined unanimously that the proposal substantially undervalues the Company and its future prospects and is not in the best interests of the Company and its stockholders. Accordingly, on November 6,2023, the Board rejected Newtyn's proposal.

The Board believes the Company is well-positioned to continue executing on its strategy and create significant long-term value for stockholders.

The information in Item 7.01 is being furnished and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any filing under the Exchange Act or the Securities Act of 1933, as amended, whether filed before or after the date hereof and regardless of any general incorporation language in such filing.

Source: https://investors.senseibio.com/static-files/3d8b9743-6449-4fd5-a60f-0a3aa0f00286

Drugmaker Novo Nordisk Seeks Obesity, Diabetes ‘Bolt-on’ Deals

Maggie Fick and Jacob Gronholt-Pedersen, Reuters, November 10, 2023 (extract)

Novo Nordisk (NOVOb.CO) wants to buy more companies with drugs in early- to mid-stages of development through "bolt-on" deals of up to a few billion dollars, CEO Lars Fruergaard Jorgensen told Reuters on Friday.

As the company's fortunes soar on demand for its popular weight-loss medicine Wegovy, Jorgensen said Novo sought to acquire companies working on medicines in the areas where it is already focused.

"So diabetes, obesity, cardiovascular disease, the whole cardiometabolic space, but also in the rare blood disorders, haemophilia, sickle cell, we believe that we have a stronghold there," he said in an interview.

"We will continuously be looking at smaller bolt-ons, typically early stage, phase 1 and phase 2, projects and typically of a very modest number of a few billion dollars," he added.

Novo's M&A strategy focuses on disease or therapeutic areas where the company has a "deep biological understanding", and also on "a set of technologies" the company wants to leverage, he added. He cited "protein engineering," saying the company had done that for year.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/drugmaker-novo-nordisk-seeks-obesity-diabetes-bolt-on-deals-2023-11-10/

Eccogene Enters Exclusive License Agreement With AstraZeneca to Develop Small Molecule GLP-1 Receptor Agonist ECC5004 for $185 Million Upfront

BOSTON and SHANGHAI, Nov. 9, 2023 /PRNewswire/ -- Eccogene announced today that it entered into an exclusive license agreement with AstraZeneca under which AstraZeneca will develop and commercialize Eccogene's small molecule GLP-1 receptor agonist (GLP-1RA) ECC5004 for the potential treatment of obesity, type-2 diabetes and other comorbidities.

"GLP-1RA represents a very important class of drugs for multiple cardiometabolic diseases; currently there is no approved orally available small molecule GLP-1RA. Small molecule GLP-1RA, such as ECC5004, could potentially offer many benefits including better convenience and ease of use compared to existing GLP-1RA therapies," said Jingye Zhou, Chief Executive Officer of Eccogene. "AstraZeneca has impressive global capabilities in clinical development and commercialization. This important collaboration between Eccogene and AstraZeneca will accelerate the development of ECC5004, a once daily, low dose, orally available small molecule GLP-1RA to benefit the millions of patients worldwide living with these diseases."

Sharon Barr, Executive Vice President, BioPharmaceuticals R&D at AstraZeneca, said: "With the number of people living with cardiometabolic conditions and obesity today already over one billion, there is a need for continued innovation and next generation therapeutic options. Building on the promising Phase I clinical data generated by Eccogene, we believe this oral GLP-1RA molecule could offer alternatives to current injectable therapies both as a potential monotherapy as well as in combination for cardiometabolic diseases such as type-2 diabetes, as well as for obesity. ECC5004 further strengthens our existing pipeline addressing both incretin and non-incretin pathways, including our GLP-1/glucagon dual agonist [AZD9550] and long-acting amylin analogue [AZD6234]."

Under the terms of the agreement, Eccogene will receive an initial upfront payment of $185 million. In addition, Eccogene will be eligible to receive up to an additional $1.825 billion in future clinical, regulatory, and commercial milestones. Eccogene is further eligible to receive tiered royalties on net product sales.

Source: https://www.prnewswire.com/news-releases/eccogene-enters-exclusive-license-agreement-with-astrazeneca-to-develop-and-commercialize-small-molecule-glp-1-receptor-agonist-ecc5004-for-cardiometabolic-diseases-301982778.html

Recursion Announces Data Deal with Tempus, Supercomputer Ambition Powered by NVIDIA, and Updated Focus of Collaboration with Bayer

SALT LAKE CITY, Nov. 09, 2023 (GLOBE NEWSWIRE)-- Recursion (NASDAQ: RXRX), a leading clinical stage TechBio company decoding biology to industrialize drug discovery, today announced two significant updates with their collaborators NVIDIA and Bayer, and a new collaboration with Tempus Labs as it creates infrastructure and expands its ambitions and scope in the precision oncology space.

"Since our founding we have believed that the next generation of biopharma leaders would operate at the intersection of scaled datasets and accelerated computing," said Chris Gibson, Ph.D., Co-founder and CEO of Recursion. "Today, we are thrilled to share three major initiatives that support this belief and our mission to bring better medicines to patients at speed and scale. With Tempus's 20 petabytes of fit-for-purpose precision oncology data, NVIDIA's support in quadrupling our supercomputing power to rapidly and reliably advance the exploration and construction of large AI models, and updating our collaboration with Bayer to rapidly pursue a set of precision oncology programs, we will continue to drive the transformation from BioTech to TechBio together."

Recursion has come to an agreement with Tempus for preferred access to one of the world's largest proprietary, de-identified, patient-centric oncology datasets, spanning DNA, RNA, health records and more to support the discovery of potential biomarker-enriched therapeutics at scale through the training of causal AI models. By combining the forward genetics approach of Tempus with the reverse genetics approach at Recursion, the company believes it has an opportunity to improve the speed, precision and scale of therapeutic development in oncology. As part of the agreement, Recursion will pay Tempus up to $160M in cash or equity over the next five years in exchange for continued and updated data access and use rights for therapeutic development purposes.

Recursion announced an updated collaboration with its established partner, Bayer, for a select set of precision oncology programs. This decision allows Bayer to leverage Recursion's state-of-the-art capabilities to identify novel targets and chemistry applicable to oncology indications. Under the terms of the agreement, the companies may initiate up to seven oncology programs and Recursion is eligible to receive potential, success-based, future payments of up to $1.5 billion plus royalties on net sales.

Source: https://www.prnewswire.com/news-releases/eccogene-enters-exclusive-license-agreement-with-astrazeneca-to-develop-and-commercialize-small-molecule-glp-1-receptor-agonist-ecc5004-for-cardiometabolic-diseases-301982778.html

Disclosure

STIFEL | Healthcare

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