Biopharmaceutical Sector

Market Update – July 24, 2023

STIFEL | Healthcare

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STIFEL | Healthcare

555 Madison Ave, Suite 1201, New York NY 10022, +1-(212) 257-5801
Web: www.stifel.com

Medical tools. Source: Getty Images.

Join Us at These Upcoming Events

1

Biotech Hangout held its latest event on July 21st.

The next event will be on July 28th.

Note that the time for the event has changed to noon EDT.

Please join us.

July 21st Replay
https://twitter.com/i/spaces/1gqxvyaAZakJB

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

2

biofuture™

New York City | October 4-6, 2023

Innovators & Investors Come Together to Shape the Future of Healthcare

At this year's summit, BioFuture attendees will be exploring the exciting mashup between rapidly evolving fields including biopharma, digital medicine, big data, AI, healthcare systems, payors, and more. The coming decade will dramatically accelerate the transformation of the healthcare ecosystem. Be part of the discussions that will shape and transform the future of healthcare.

To Learn More
https://biofuture.com/

Macro Update

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

Inflation Rarely Falls This Fast. What It Means for the Stock Market

Ben Levisohn, *Barron's*, July 18, 2023

"After more than two years of rising prices, the rate of inflation is falling—and fast. The consumer price index rose just 3% in June from the prior year, its smallest increase since March 2021. It's down 6.1 percentage points in the past 12 months, marking the largest such decline since 2009, when inflation had turned to deflation. The last time the rate of CPI fell from above 9% by 6.1 percentage points, or more was in May 1952, when the index dropped 7.4 points to 1.9%.

Let's consider how big an accomplishment this is. Yes, the overall inflation numbers remain too high. Core CPI, which removes food and energy from the equation, sits at 4.8%, well above the Fed's target of 2%, and average hourly earnings continue to grow at a 4.4% clip.

But there's a truism investors should fall back on: It's the direction, not the level. And since the direction of inflation is down, the direction of the stock market is up. It really is that simple, and it's a big part of why the stock market has raced higher in 2023."

Source: https://www.barrons.com/articles/inflation-history-stock-market-6c73938b

Fed Looks Set To Raise Rates In July

Simon Moore, *Forbes*, July 19, 2023

"Markets have high confidence that the Federal Reserve will raise rates 0.25-percentage-points at their next interest rate decision on July 26. The Fed suggested this during their June decision, which held rates steady. The June economic projections signaled a base case of two more hikes from the four remaining Fed meetings of 2023. In addition, the June statement explicitly referenced "additional policy firming" and during his press conference Jerome Powell offhandedly referred to the June decision as a "skip", perhaps implying that the June decision was a pause between hikes rather than a more fundamental change in direction for interest rates.

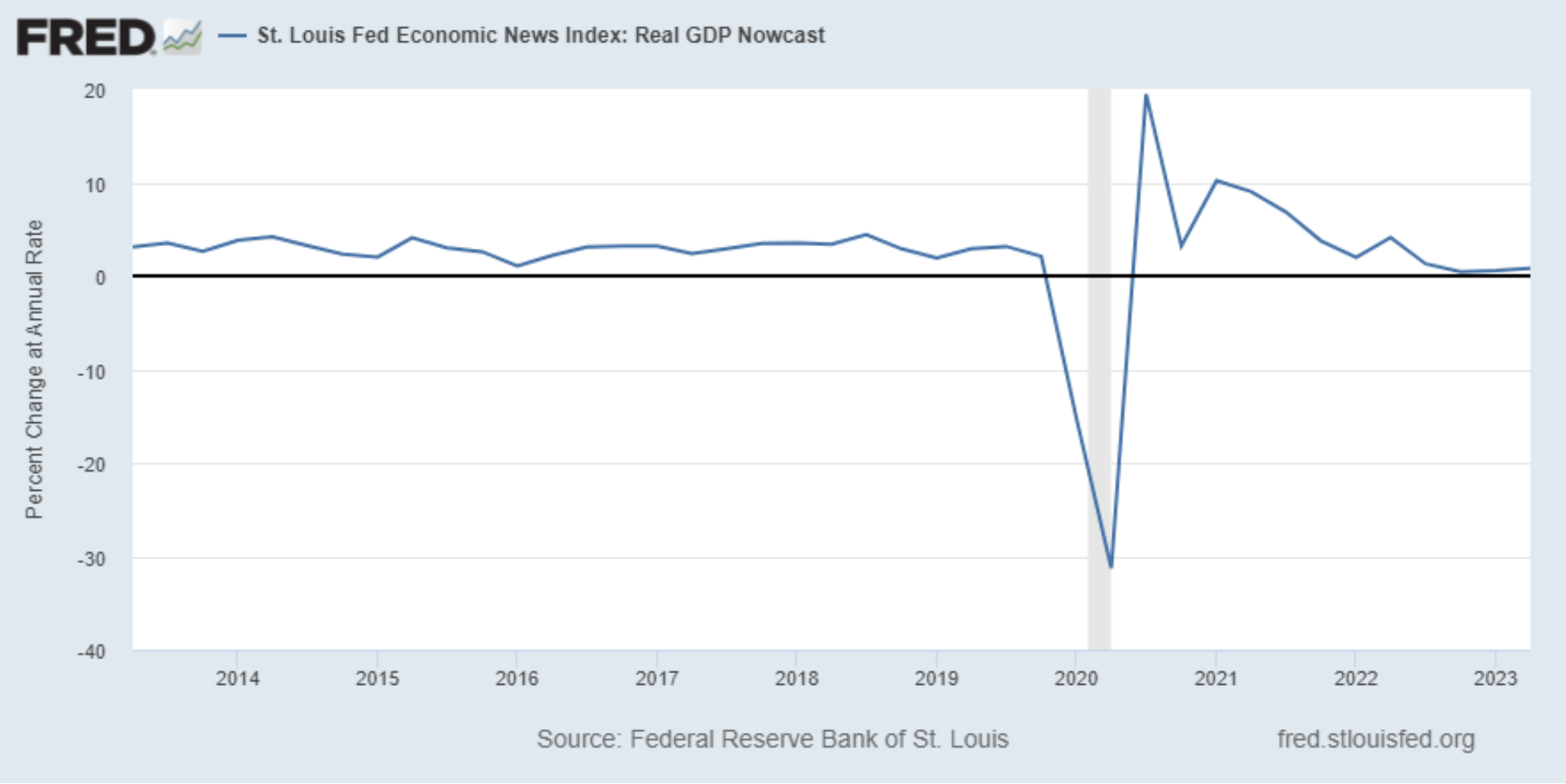
In a speech on July 13, Fed Governor Christopher Waller clearly spelled out the Fed's likely actions saying, "I see two more 25-basis-point hikes in the target range over the four remaining meetings this year as necessary to keep inflation moving toward our target." Importantly, this speech came after June's CPI data, which showed more evidence of disinflation, but apparently that hasn't changed the Fed's resolve at this point."

It's starting to look like the end of the Fed tightening cycle is in sight.

Source: https://www.forbes.com/sites/simonmoore/2023/07/19/fed-appears-set-to-raise-rates-in-july-but-here-are-the-details-that-matter

We Continue to Avoid Recession

St. Louis Fed's Economic News Index (ENI) uses economic content from key monthly economic data releases to forecast the growth of real GDP during that quarter. In general, the most-current observation is revised multiple times throughout the quarter. The final forecasted value (before the BEA's release of the advance estimate of GDP) is the static, historical value for that quarter.



The St. Louis Fed has a high-performing forecasting tool for next quarter's change in GDP. As of July 21, the model is saying that we will come close to zero growth but not dip into the negative (recession).

Source: https://fred.stlouisfed.org/graph/?g=17f3e

An ‘Immaculate Disinflation’ In The US Is Not Guaranteed

***Excerpt from Editorial, Financial Times*, July 23, 2023**

“The US Federal Reserve may feel a little smug this week as its interest rate setting committee meets for the last time before the summer break. Annual inflation in America slowed to just 3 per cent in June, the lowest since March 2021. It has dropped below even the traditionally inflation-challenged Japan, where price growth has hit 3.3 per cent. Perhaps more impressive is that joblessness has barely increased, and the odds of a recession are falling, despite the Fed’s aggressive 500 basis points of rate rises over the past 18 months.

Can chair Jay Powell really pull-off an “immaculate disinflation” of the US economy? If he did, it would make him one of the more successful Fed chiefs.

Even the lauded Paul Volcker — who famously pushed interest rates up to 19 per cent in the early 1980s — ended up propelling US unemployment to its then highest since the Great Depression.

Economic activity is resilient. This month consumer sentiment reached a near two-year high. Markets are expectant too. A swath of US stocks, not just tech firms, have rallied. But a “soft landing” — when inflation is brought down without triggering a significant downturn — is far from guaranteed.”

Inflation still poses a recessionary risk to the economy.

Source: https://www.ft.com/content/787426e2-e658-4dc3-a791-e00ccea2fab2. Photo from Getty Images.

Biopharma Market Update

Healthcare market montage. Source: Getty Images.

Biotech Stocks Flat Again Last Week

The XBI was up last week by 0.7%. The XBI is up 2.4% for the year and our tracker of biotech aggregate value is up 4.4% for the year to date. The Nasdaq Biotech Index remains down for the year while the S&P 500 is now up 18.1%.

Biotech Stocks Down Last Week

Return: July 15 to July 21, 2023

Nasdaq Biotech Index: +1.7%
Arca XBI ETF: +0.65%
Stifel Global Biotech (EV): -0.2%*
S&P 500: +1.7%

Return: Jan 1 to July 21, 2023

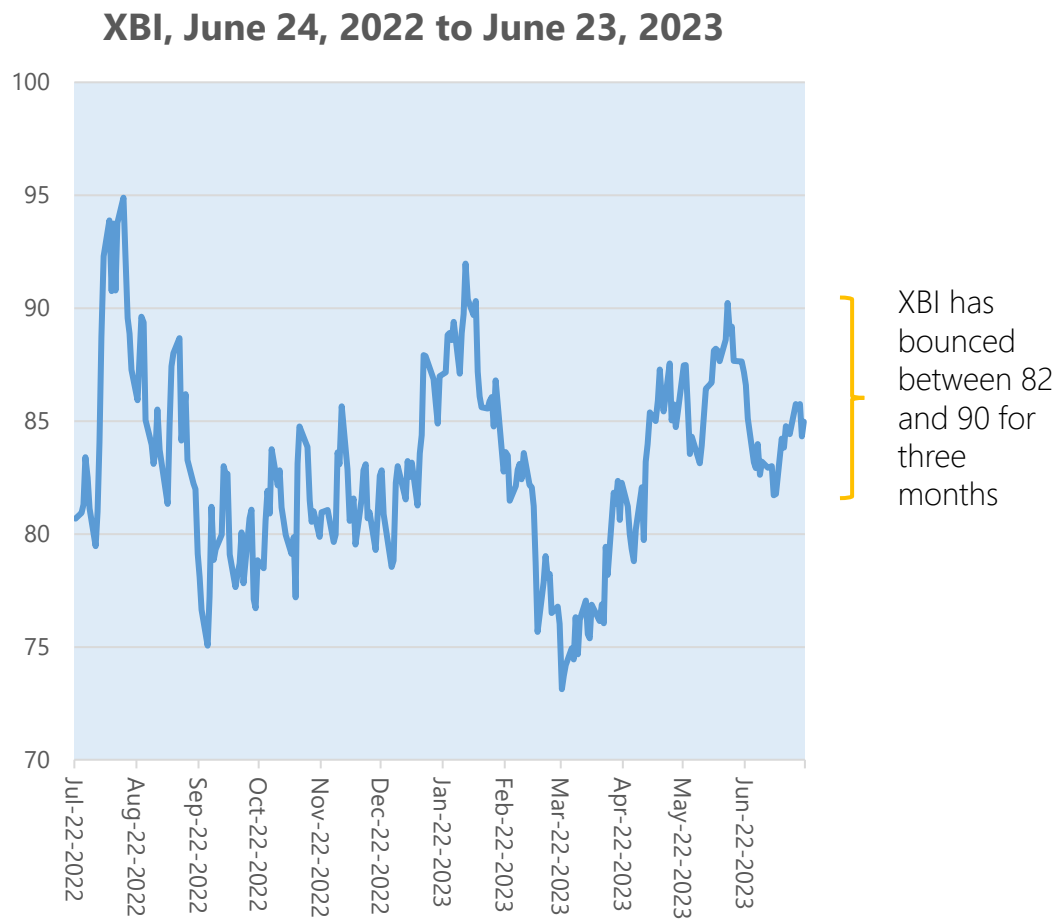
Nasdaq Biotech Index: -1.0%
Arca XBI ETF: +2.4%
Stifel Global Biotech: +4.4%*
Stifel Global Biotech (adjusted): +11.3%
S&P 500: +18.1%

VIX Flat and Low

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
Apr 28: 15.8%
May 26: 18.0%
June 9: 13.7%
June 23: 13.4%
July 21: 13.6%

10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
Apr 28: 3.44%
May 26: 3.8%
June 9: 3.75%
June 23: 3.74%
July 21: 3.84%



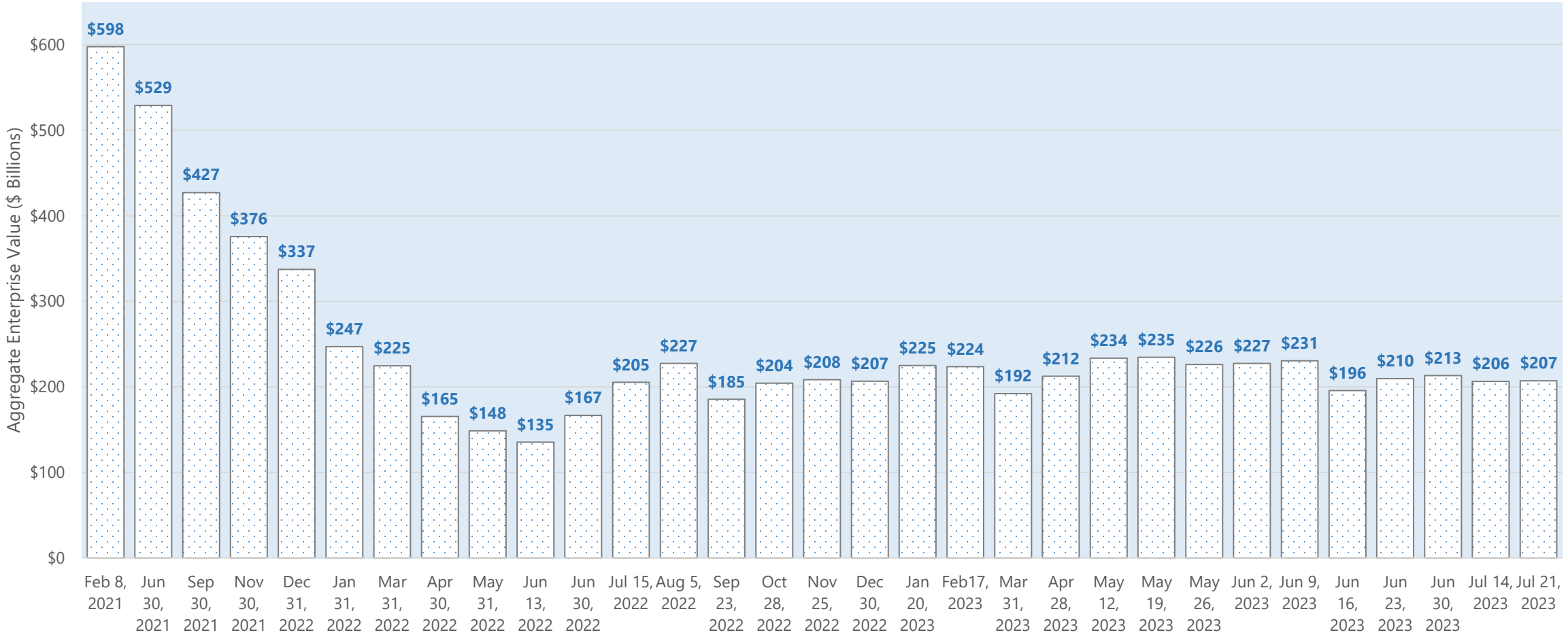
* Change by enterprise value.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Valuation Flat Last Week

The total value of the global biotech sector was flat last week. However, we added in companies that recently went public and removed Iveric and Vectiv – which distorts the data.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Jul 21, 2023 ($ Billions)



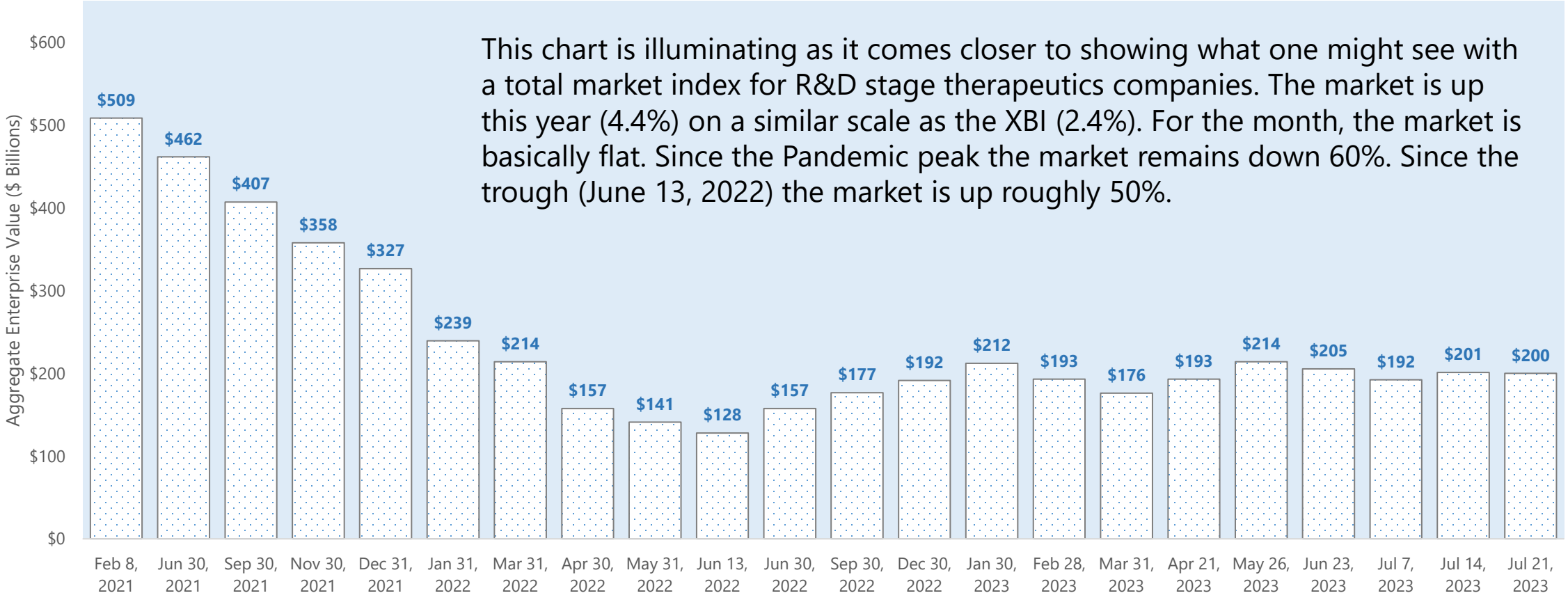
Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange.

Survival Adjusted Biotech Valuations Up 4.4% This Year

This chart only includes biotech companies that are on the market today and were trading at the start of the year. This shows the value of these companies going back to market peak (Feb 8, 2023). Of course, an investor would have had a higher capital gain from buying the market biotech portfolio on Dec 31, 2023 due to M&A exits.

Total Enterprise Value of Publicly Traded Global Biotech

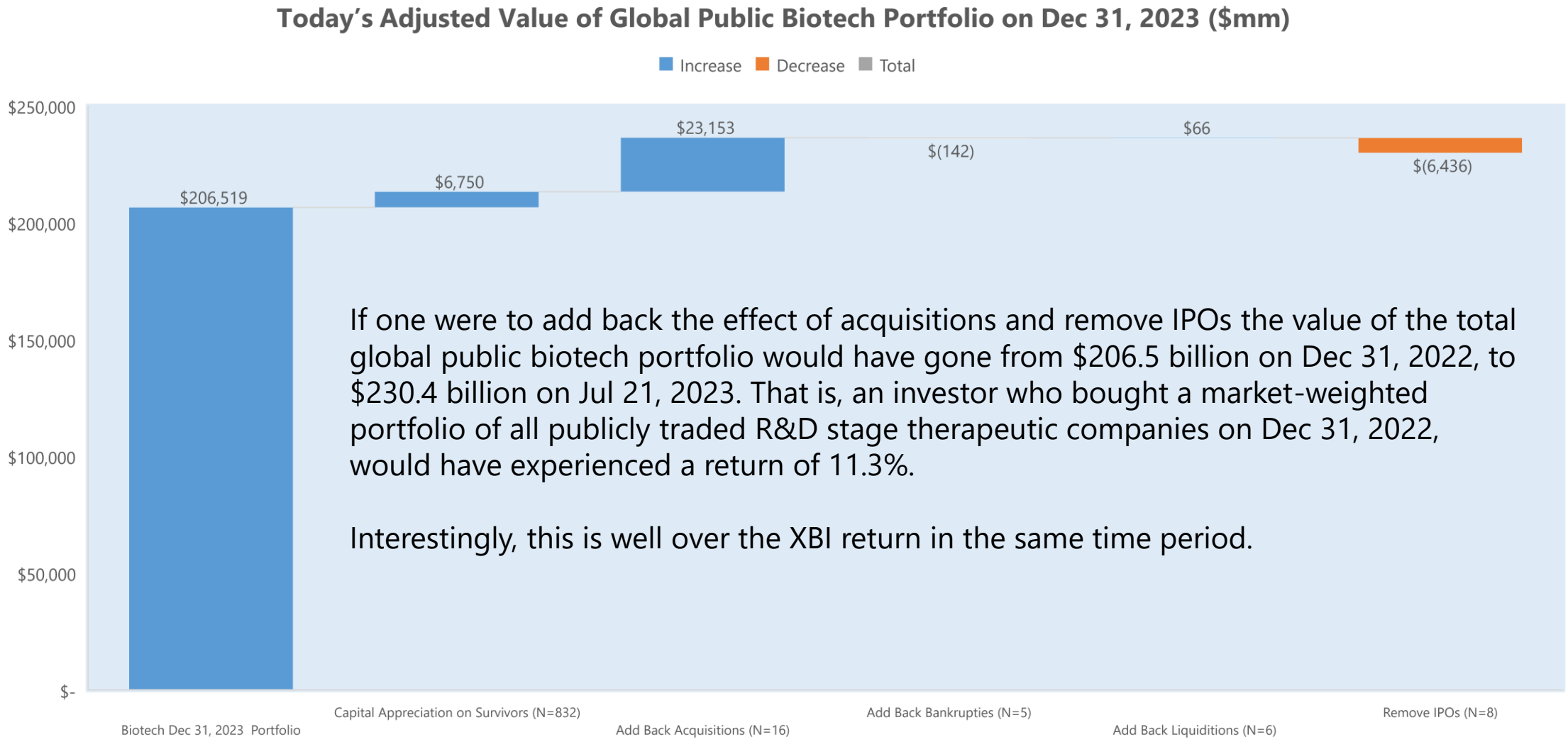
(Cohort that Existed on Jul 21 and Jan 1, 2023), Feb 8, 2021 to Jul 21, 2023 ($ Billions)



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

Estimate of YTD Capital Gain From Holding the Market Biotech Portfolio

We added back in the effect of M&A exits, subtracted out the effect of IPOs and adjusted for bankruptcies and liquidations. All eight reverse mergers were carried forward, matching new names with the prior shell company.



If one were to add back the effect of acquisitions and remove IPOs the value of the total global public biotech portfolio would have gone from $206.5 billion on Dec 31, 2022, to $230.4 billion on Jul 21, 2023. That is, an investor who bought a market-weighted portfolio of all publicly traded R&D stage therapeutic companies on Dec 31, 2022, would have experienced a return of 11.3%.

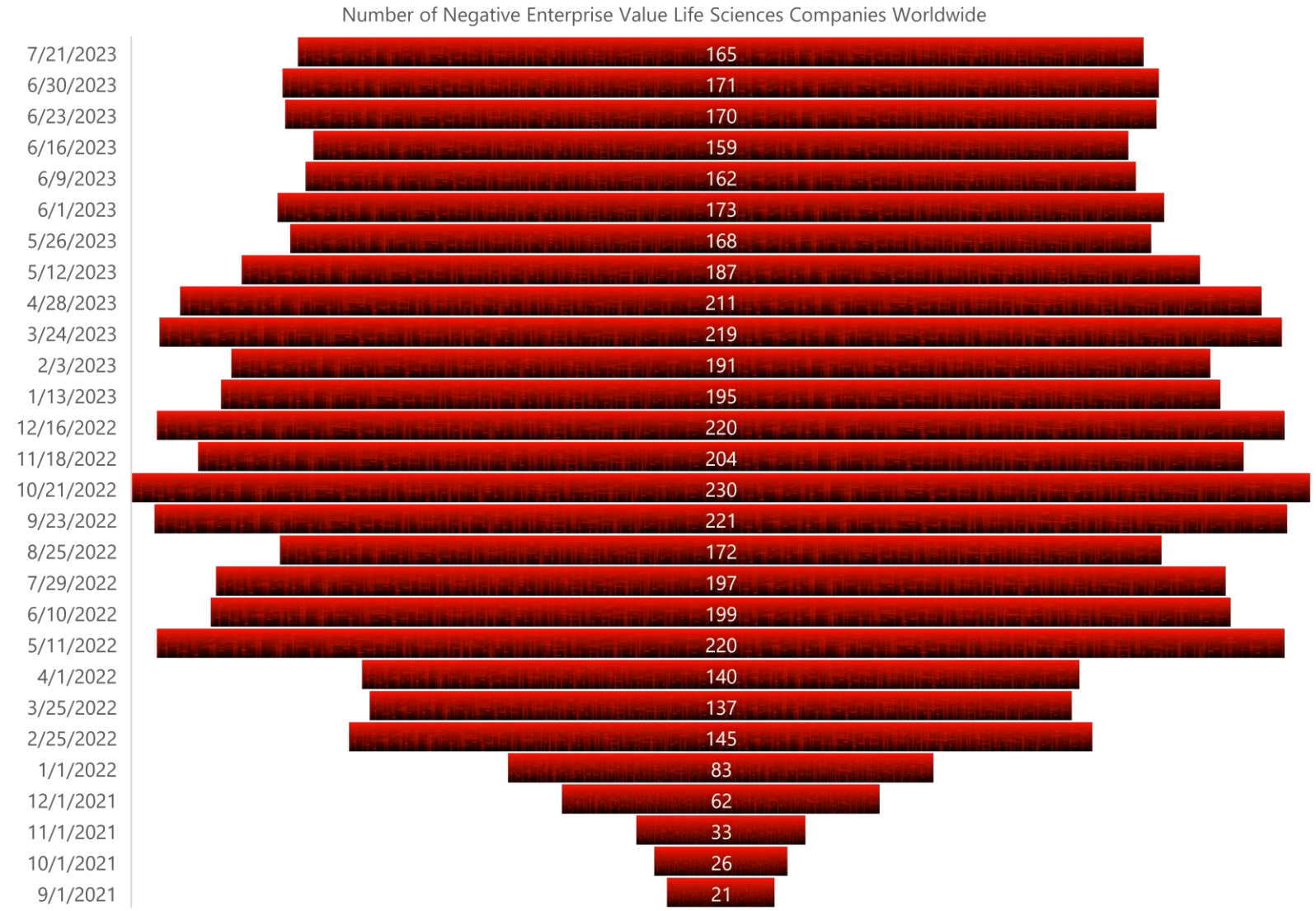
Interestingly, this is well over the XBI return in the same time period.

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

Companies that Disappeared From the Public Biotech List Thus Far in 2023

Company Name	Disposition	Net Effect on Portfolio Value ($mm)
Prometheus Biosciences	Bought by Merck	$10,163
IVERIC bio	Bought by Astellas	$5,424
Provention Bio	Bought by Sanofi	$2,784
BELLUS Health	Bought by GSK	$1,668
Imago BioSciences	Bought by Merck	$1,169
VectivBio	Bought by Ironwood	$959
Concert Pharmaceuticals	Bought by Sun Pharma	$693
Satsuma Pharmaceuticals	Bought by SNBL	$180
Opiant Pharmaceuticals	Bought by Indivior	$145
F-star Therapeutics	Bought by Sino Bio	$102
Codiak BioSciences	Bankruptcy	$23
Metacrine	Liquidating	$21
Rubius Therapeutics	Liquidated	$20
Sio Gene Therapies	Liquidated	$18
Calyxt	Merged into Cibus	$14
Surface Oncology	Bought by Coherus	$11
PolarityTE	Bankruptcy	$10
Ayala Pharmaceuticals	Merged into Advaxis	$5
Oncorus	Liquidated	$5
Calithera Biosciences	Liquidating	$2
Pherecydes Pharma	Merged into Ethypharm	$0
Lysogene	Liquidating	-$10
4D pharma	Bankruptcy	-$28
Jounce Therapeutics	Bought by Concentra	-$82
TCR2 Therapeutics	Bought by Adaptimmune	-$83
Tricida	Bankruptcy	-$137

Number of Negative Enterprise Value Life Sciences Companies Fell in Last Three Weeks



The count of negative EV life sciences companies worldwide has crept down from 171 three weeks ago to 165 last Friday.

Source: CapitalIQ

Public Life Sciences Sector Value Dropped Last Week

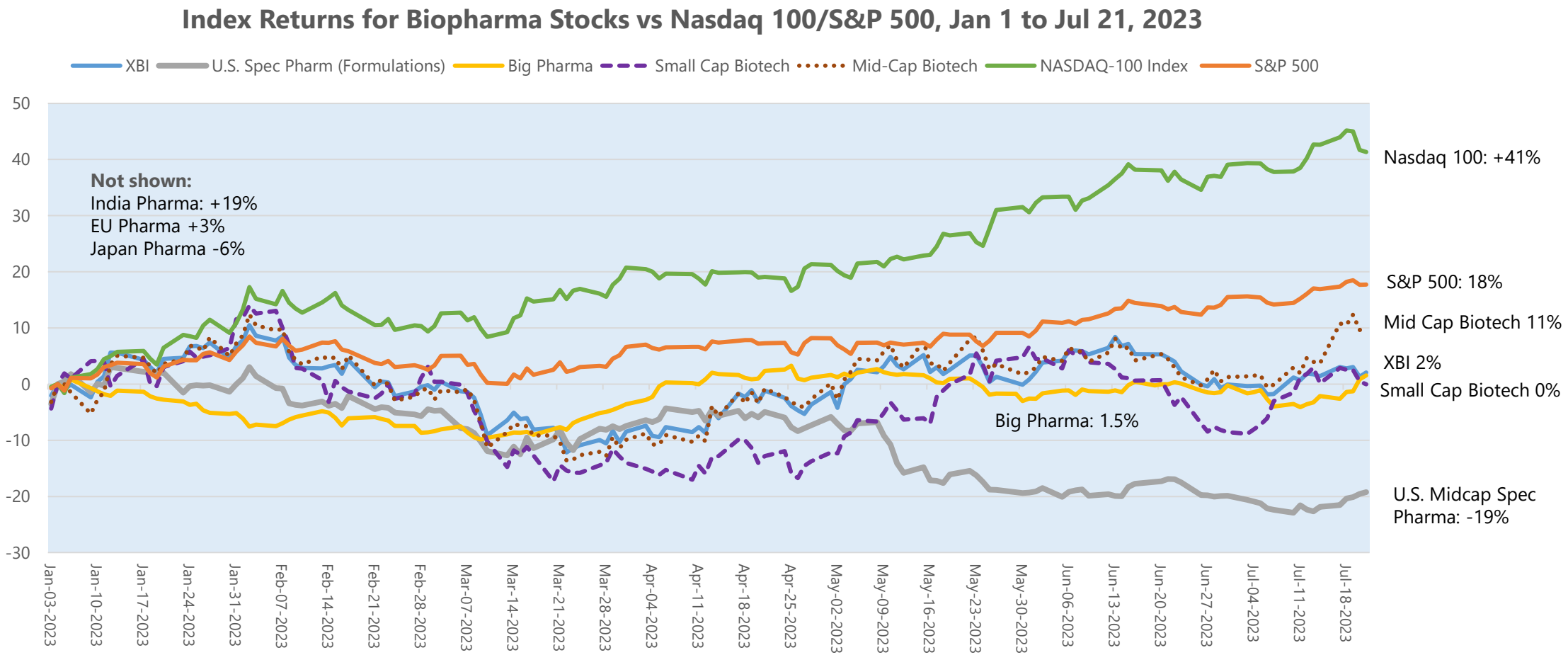
The total enterprise value of the publicly traded life sciences sector rose by 1.8% last week ($126 billion). The sectors that declined the most were HCIT and CDMO's. Commercial Pharma and LS Tools performed well.

Sector	Firm Count	Enterprise Value (July 21, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$79,014	-0.1%	2.8%	-12.7%
Biotech	828	$232,650	-0.2%	-0.9%	15.7%
CDMO	40	$168,962	-3.0%	1.0%	-21.8%
Diagnostics	83	$285,554	-0.6%	3.9%	16.4%
OTC	32	$30,732	0.4%	0.7%	15.0%
Pharma	727	$5,886,682	2.5%	0.8%	4.5%
Services	41	$210,772	0.1%	4.2%	-14.0%
Tools	54	$740,569	5.5%	6.7%	-5.1%
Devices	183	$1,730,919	-0.6%	0.9%	7.3%
HCIT	11	$27,374	-2.2%	8.4%	-15.8%
Total	**2080**	**$9,376,807**	**1.8%**	**1.4%**	**3.4%**

Source: CapitalIQ

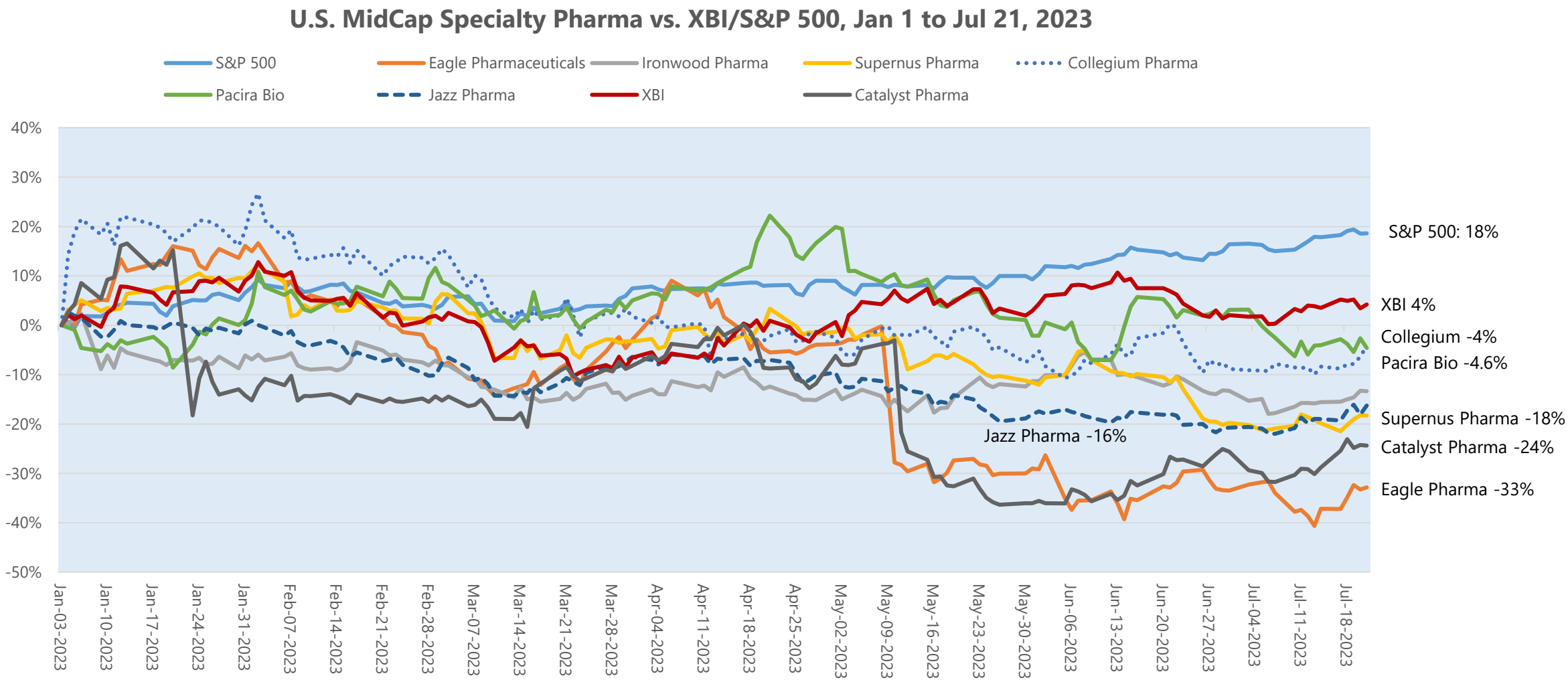
Tech Stocks Have Trounced Biopharma This Year

The gap between the tech-heavy Nasdaq 100 Index and the XBI is now 39 percentage points for the year. The S&P 500 is up 18% due its tech content. Mid-cap biotech is up 11%; small cap biotech is flat, and U.S. mid-cap spec pharma is down 19%.



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. U.S. Midcap Pharma includes EGRX, COLL, CPRX, PCRX, IRWD, JAZZ, SUPN. Mid-cap biotech includes Index: LEGN, IONS, ARWR, CRSP, NTLA, CERE, CYTK, KRTX, DNLI, TPTX, VIR, BBIO, BEAM, MRTX, ZLAB, FATE, IBRX, IMCR, IOVA, XENE, RLAY, ZNTL, KRYS, ARVN, ALLO, RVMD, XNCR, TBPH, DAWN, SANA, BLTE, PCVX, SWTX, ARQT, MDGL, ISEE and RXRX.

U.S. MidCap Specialty Pharma Having a Tough Year



Source: CapitalIQ

Artificial Intelligence Boom Generates Optimism in Tech Sector as Stocks Soar

Dan Milmo, Technology Editor, *The Guardian*, July 22, 2023

US tech companies started the year in the doldrums, beset by a cost overhang from excessively zealous pandemic hiring sprees and fears about the impact of rising interest rates. Things were looking grim – then along came artificial intelligence (AI).

Tech stocks and the blue-chip S&P 500 index have since been buoyed by breakthroughs in generative AI – led by the ChatGPT chatbot – and the promise of a new era of growth for the sector. The S&P 500 is up 18.6% so far in 2023 while the tech-heavy Nasdaq composite is up 35.7%. Six months is a long time in a fast-moving industry.

Five of the biggest beneficiaries of the US tech resurgence report quarterly results over the next two weeks: Facebook owner Meta, Google parent Alphabet, Apple, Amazon and Microsoft.

Each has individual factors at play in their recent stock performances, but the AI frenzy has provided a general lift to the sector. Chipmaker Nvidia, which reported its three-monthly results in May, is the emblem of the revival – becoming a $1tn company off demand for its products to provide processing power for the new technology.

Source: https://www.theguardian.com/technology/2023/jul/23/artificial-intelligence-boom-generates-optimism-in-tech-sector-as-stocks-soar; Photo: Getty Images.

The Bear Market Has Nearly Been Erased, Fewer Than 20 Months After It Began

- **S&P 500 closer to erasing 2022's loss after nine-month rally**
- **Gains in risky assets reflect growing optimism in soft landing**

Lu Wang and Isabelle Lee, Bloomberg, July 21, 2023

"It made sense at the time. Jerome Powell was waging war on inflation. The bond market was flashing dire warnings. Practically everyone saw a recession coming.

And yet fewer than 20 months after it began, the bear market that engulfed the S&P 500 is a mere 260 points from being completely erased. Rather than foretelling trouble, chart patterns tracking everything from cross-asset momentum to transportation companies are painting a picture of burgeoning economic vigor."

The tech stock boom has had the effect of largely reversing the 2022 loss in the S&P 500 Index.

In contrast, obviously, the XBI remains way down from its previous 2021 peak.

Source: https://www.bloomberg.com/news/articles/2023-07-21/s-p-500-s-great-bear-market-unwinding-is-happening-at-a-frenetic-clip

Industry News

Lab discussion over experiment: Getty Images.

Talks Between FTC and Amgen Have Broken Off

July 19, 2023 (Bloomberg) - The Federal Trade Commission said that there are no ongoing talks with Amgen Inc. to resolve a legal challenge to it $27.8 billion takeover of Horizon Therapeutics Plc after the agency rejected a settlement overture made earlier this year.

During a hearing Wednesday in the FTC's in-house court, agency lawyer Nathan Brenner said the FTC engaged in settlement discussions earlier in the case and remains "open to hearing proposals."

David Marriott, a lawyer for Amgen, acknowledged the earlier talks but said the company believes there is "no anticompetitive effect" by the deal to fix.

Source: https://www.bloomberg.com/news/articles/2023-07-19/ftc-says-amgen-horizon-deal-block-settlement-talks-have-ended

FTC Has Made Second Request on Pfizer/Seagen Deal

July 14, 2023 (Reuters) - The US Federal Trade Commission (FTC) has sought additional information and documentary material related to Pfizer's (PFE.N) proposed acquisition of Seagen Inc (SGEN.O), Seagen said on Friday.

The antitrust agency sent the requests separately to both the companies, a regulatory filing said.

Pfizer struck a $43 billion deal in March to acquire Seagen and its targeted cancer therapies, to counter the fall in COVID-related sales and generic competition for some top-selling drugs.

Source: https://www.reuters.com/markets/deals/us-ftc-seeks-additional-info-pfizers-proposed-takeover-seagen-2023-07-14/

Editorial: EU Pharma Reforms will Hurt Patients and Hinder Research

Annette Bakker, President of the Children's Tumor Foundation, *Politico*, July 20, 2023

"The European Commission recently proposed its first major overhaul of European Union pharmaceutical policies in two decades.

The proposed reforms take a carrot-and-stick approach, shortening the duration of market exclusivity for new medications, thus allowing cheaper generic drugs on the market two years sooner.

The threat of massive revenue loss caused by generic competition is the stick here. The fact that drugmakers could earn back most of those two protected years by introducing their new medicines in all 27 EU member countries within a certain time frame, and by developing medications that address an "unmet medical need," is the carrot.

But while the proposal could offer an even lengthier overall regulatory protection period than the current regime, the strict conditions linked to obtaining full protection are unlikely to be matched by pharmaceutical companies. And rather than resulting in more and faster drug launches, the proposed approach will likely result in fewer launches and less research taking place on the Continent.

Even if biotech firms were to launch in all 27 member countries, it's ultimately up to the individual states — which have to set the price and reimbursement for a drug before it debuts on the market — to determine when a medicine launches. And many of them routinely fail to conclude pricing negotiations in a timely manner, creating far too much uncertainty around the proposed reforms."

Source: https://www.politico.eu/article/european-union-pharmaceutical-reforms-hurt-patients-hinder-research/

Bill in Congress to Bring Obesity Drug Coverage to Medicare

Eric Sagonowsky, *Fierce Pharma*, July 20, 2023

Despite the widespread hype surrounding new and powerful obesity medicines, the drugs are still out of reach for many Americans who could benefit.

One reason is that under current laws, Medicare is barred from covering obesity drugs. But under legislation backed by Novo Nordisk, Eli Lilly, Boehringer Ingelheim and many other organizations, a group of lawmakers aims to change that.

Sens. Bill Cassidy, M.D., R-Louisiana, and Tom Carper, D-Delaware, plus Reps. Brad Wenstrup, R-Ohio, and Raul Ruiz, D-California, have proposed the Treat and Reduce Obesity Act, which would step up the government's fight against the obesity epidemic.

As the lawmakers note, many common conditions such as heart disease and diabetes are associated with obesity. They say the bill would "work to directly prevent these comorbidities through expanded coverage of new health care specialists and chronic weight management medications for Medicare recipients."

"There is a clear need to address obesity," Cassidy said in a Thursday statement. "Expanding Medicare coverage to the treatments patients need enables them to improve their health and benefits us all."

Source: https://www.fiercepharma.com/pharma/novo-nordisk-eli-lilly-and-boehringer-get-behind-lawmakers-bill-enable-obesity-drug-coverage

Novartis Sales Growth in Q2 From Growth Drivers Impressive

Q2 growth driven by strong performance from Entresto®, Kesimpta®, Pluvicto® and Kisqali®

Q2 sales

	Sales USD million	Growth vs. PY USD million	Growth vs. PY cc
Entresto	1,516	391	37%
Kesimpta (ofatumumab)	489	250	105%
PLUVICTO	240	230	nm
KISQALI ribociclib	493	185	66%
SCEMBLIX	106	75	248%
LEQVIO	78	56	249%
LUTATHERA	150	64	75%
PROMACTA (eltrombopag)	583	49	11%
PIQRAY	130	45	54%
Tafinlar + Mekinist	496	44	13%
ILARIS (canakinumab)	316	41	17%

Strong growth (+71% cc); expected to continue

Constant currencies (cc) is a non-IFRS measure; explanation of non-IFRS measures can be found on page 48 of Condensed Interim Financial Report. Unless otherwise noted, all growth rates refer to same period in PY.
nm – not meaningful.

Source: https://www.novartis.com/news/novartis-financial-results-q2-2023

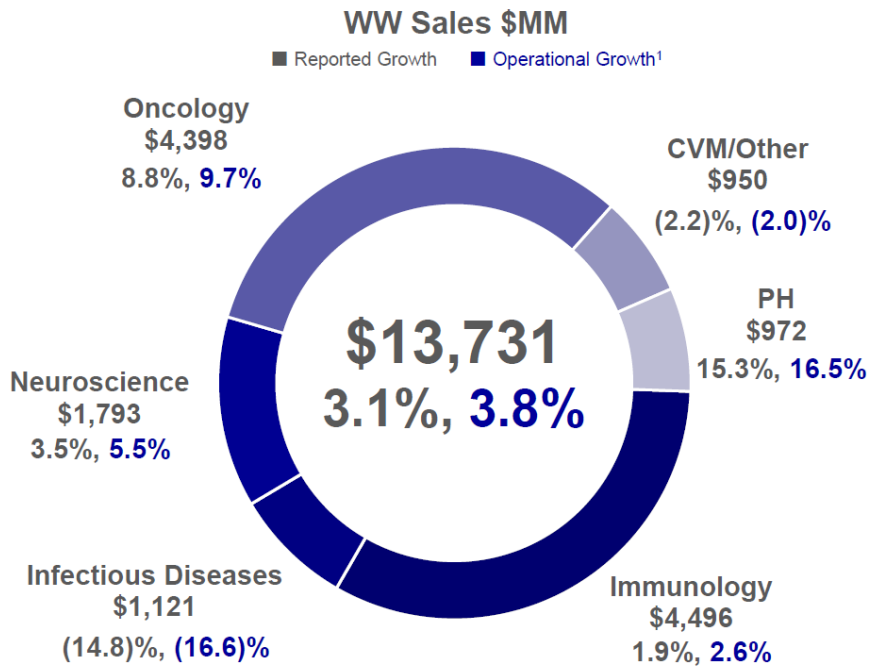
J&J Q2 Pharma Results Driven by Oncology and Immunology (Especially Darzalex® and CARVYKTI®)

Pharmaceutical Highlights – 2nd Quarter 2023

Strong operational growth[1] of 6.2% excl. COVID-19 Vaccine driven by Oncology, Immunology, and PH

Reported: WW 3.1%, U.S. 9.2%, Int'l (4.0)%

Operational[1]: WW 3.8%, U.S. 9.2%, Int'l (2.5)%



Key Drivers of Operational Performance[1]	
Immunology	• STELARA increase driven by market growth partially offset by unfavorable patient mix and rebates • Growth in TREMFYA due to share gains and market growth, partially offset by unfavorable patient mix • REMICADE decline due to biosimilar competition
Infectious Diseases	• COVID-19 Vaccine revenue decline
Neuroscience	• SPRAVATO growth driven by ongoing launches in the U.S. and Europe • Growth partially offset by declines from the paliperidone long-acting injectables, due to the XEPLION loss of exclusivity in EU
Oncology	• DARZALEX increase driven by share gains in all regions and continued market growth • Continued share gains and market growth in mCSPC, and increased penetration from new launches for ERLEADA • CARVYKTI increase driven by continued market share gains from ongoing launch • Growth partially offset by ZYTIGA loss of exclusivity and IMBRUVICA decline due to global competitive pressure. Imbruvica maintains its market leadership position
Cardiovascular/ Metabolism/ Other (CVM/Other)	• XARELTO increase due to favorable patient mix and market growth, partially offset by share loss
Pulmonary Hypertension (PH)	• Increase driven by favorable patient mix, share gains, and market growth from UPTRAVI and OPSUMIT • Continued declines in Other Pulmonary Hypertension

Adjusted Operational Sales[2]: WW 3.9%, U.S. 9.2%, Int'l (2.2)%

13

Johnson & Johnson

[1] Non-GAAP measure; excludes the impact of translational currency; see reconciliation schedules in the Investors section of the company's website
[2] Non-GAAP measure; excludes acquisitions and divestitures and translational currency; see reconciliation schedules in the Investors section of the company's website
Note: Values may not add due to rounding

DARZALEX · DARZALEX Faspro · CARVYKTI · Spravato · Uptravi · Symtuza · Opsumit · Xarelto · Erleada · Stelara · Simponi · imbruvica · INVEGA SUSTENNA · Tremfya

Source: https://johnsonandjohnson.gcs-web.com/events-and-presentations

Vir Reports Unsuccessful Phase 2 Study in Flu – Stock Down

Vir Biotechnology Announces Topline Data from Phase 2 PENINSULA Trial Evaluating VIR-2482 for the Prevention of Seasonal Influenza A Illness

SAN FRANCISCO, July 20, 2023 (GLOBE NEWSWIRE) -- Vir Biotechnology, Inc. (Nasdaq: VIR) today announced that the Phase 2 PENINSULA (PrevEntioN of IllNesS DUe to InfLuenza A) trial evaluating VIR-2482 for the prevention of symptomatic influenza A illness did not meet primary or secondary efficacy endpoints. In participants who received the highest dose of VIR-2482 (1,200 mg), a non-statistically significant reduction of approximately 16% in influenza A protocol-defined illness was observed. Participants who received the highest dose showed an approximately 57% reduction in symptomatic influenza A illness, when defined according to CDC influenza-like-illness criteria, which was one of two secondary endpoints. VIR-2482 was generally well tolerated and no safety signals were identified.

Source: https://investors.vir.bio/news-releases/news-release-details/vir-biotechnology-announces-topline-data-phase-2-peninsula-trial

Merck Gets Positive CHMP Opinion for Approval its Cough Drug (Gefapixant)

RAHWAY, N.J.--(BUSINESS WIRE)-July 21, 2023- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended the approval of gefapixant, an investigational, non-narcotic, oral selective P2X3 receptor antagonist, developed for the treatment for adults with refractory or unexplained chronic cough. The CHMP's recommendation will now be reviewed by the European Commission (EC) for marketing authorization in the European Union (EU) and a final decision is expected later this year.

"Today's positive CHMP opinion is the next step for gefapixant to become the first treatment approved in the European Union for adults with refractory or unexplained chronic cough," said Dr. Joerg Koglin, senior vice president, global clinical development, Merck Research Laboratories. "Refractory or unexplained chronic cough as a condition with often disruptive, uncontrolled coughing associated with major physical, social and emotional consequences represents a large unmet clinical need."

The CHMP's positive opinion is based on results from the COUGH-1 and COUGH-2 clinical trials, which are the first companion Phase 3 studies ever completed in patients with refractory or unexplained chronic cough, a cough that persists despite appropriate treatment of underlying conditions or for which the underlying cause cannot be identified despite a thorough evaluation. Both studies met the primary endpoint, demonstrating a statistically significant reduction in 24-hour cough frequency in adults treated with gefapixant 45 mg twice daily versus placebo at 12 weeks (COUGH-1) and 24 weeks (COUGH-2).

Source: https://www.merck.com/news/merck-receives-positive-european-union-chmp-opinion-for-gefapixant/

Experts Flag Eye Inflammation Reports Tied to Apellis' Geographic Atrophy Med Syfovre

Zoey Becker, *Biopharma Dive*, Jul 17, 2023

Apellis Pharmaceuticals' Syfovre, after achieving the first FDA approval for advanced eye disease geographic atrophy, has been associated with rare but severe side effects, according to the American Society of Retinal Specialists (ASRS).

The group issued a letter to doctors Saturday flagging cases of eye inflammation and six reports of occlusive retinal vasculitis in patients who took the drug, BioPharma Dive reported. The condition is a type of inflammation that blocks blood flow to the retina and could potentially cause blindness.

ASRS didn't tie the safety issues to a specific batch of product but noted that the side effects began one to two weeks after a patient's first Syfovre injection. The organization urged vigilance and close follow-up after administration, according to the news outlet.

Source: https://www.fiercepharma.com/pharma/experts-flag-eye-inflammation-reports-tied-apellis-geographic-atrophy-med-syfovre

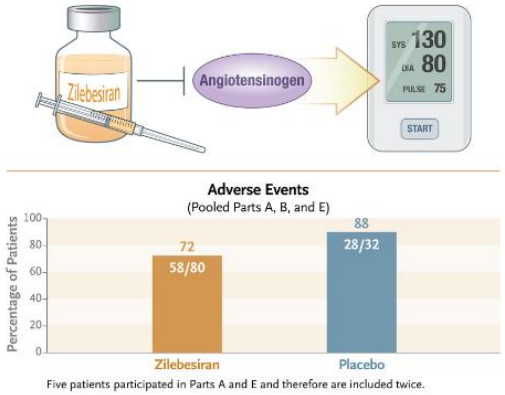
RNAi from Alnylam Achieves Sustained BP Lowering

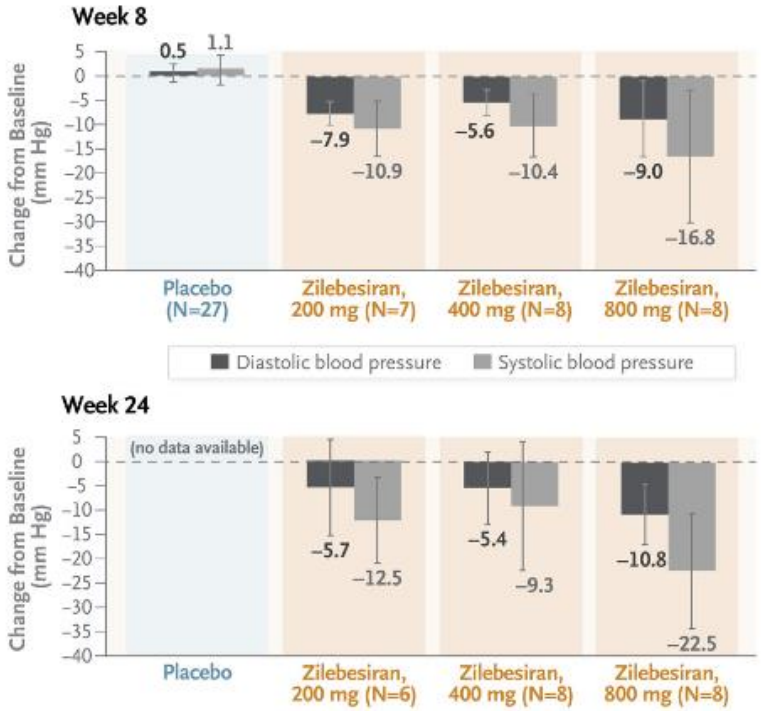
Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.

New England Journal of Medicine, June 21, 2023

Despite effective therapeutic options, nearly half the patients with hypertension do not reach guideline-recommended blood-pressure targets, partly as a consequence of physician failure to initiate or intensify antihypertensive therapy and poor patient adherence to prescribed daily oral medications. Even when blood pressure appears to be well managed on the basis of intermittent office measures, control may remain suboptimal owing to marked variability in blood pressure over the diurnal cycle and in the long term. In this phase 1 study involving patients with hypertension, we observed dose-related decreases in both serum angiotensinogen levels and blood pressure after single subcutaneous doses of zilebesiran that were sustained for up to 24 weeks. Among the treatment-related adverse events that were observed, the most common were mild, transient injection-site reactions.





Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2208391

Big Global Opportunity for RNAi for Blood Pressure Control

Xu et.al., "Interventions to improve medication adherence among Chinese patients with hypertension: a systematic review and meta-analysis of randomized controlled trials," Int J Pharm Pract. 2018 Aug;26(4):291-301.

Hypertension is one of the major public health issues around the world and is among the major modifiable risk factors of cardiovascular diseases. The World Health Organization (WHO) reported that hypertension is estimated to have caused 9.4 million deaths and 7% of the disease burden in 2010, and the situation is still deteriorating. In China, the prevalence of hypertension is 32.5%. About one-third of Chinese adults need antihypertensive treatment, but only 46.4% of them are being treated with anti-hypertensive medications, resulting in an overall control rate of 4.2%. **Nonadherence to antihypertensive medication is the main reason for the ineffective control of blood pressure.** One study had shown that patients' adherence to their medication regimen reduces the risk of myocardial infarction by 20%–25%, cardiac failure by >50%, and stroke by 35%–40%. **Nonadherence to medication regimens is common among patients with hypertension worldwide, especially in China, with nonadherence rate ranged from 40.3% to 78.7%.**

Source: https://pubmed.ncbi.nlm.nih.gov/29693291/

Hypertension Control is a Huge Global Opportunity to Save Lives: China Example

Frieden TR. China Can Substantially Reduce Its High Burden of Stroke and Heart Attack. *China CDC Wkly*. 2020 Oct 2;2(40):780-782.

Hypertension, the leading cause of cardiovascular disease, kills 10.7 million people worldwide each year — more than any other cause, and more than all infectious diseases combined. Approximately one third of adults globally have elevated blood pressure; of these approximately 1.4 billion people, only 1 in 7 with hypertension are effectively treated so that their blood pressure is reduced to below 140/90.

China's hypertension burden mirrors the global situation**. A quarter of a billion people in China have hypertension — the most of any country in the world** — with 23.5% of the adult population having elevated blood pressure. Only an estimated 10%–15% of those with hypertension are treated effectively such that they have the condition under control.

Each year, 1.8 million people in China die from hypertension, nearly double the number in India despite similar population sizes and rates of hypertension. For a productive and healthy future, prevention and control of hypertension is essential.

Of all primary care interventions for adults, improvement in control of hypertension can save the most lives, potentially many times the number from many other interventions.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8393027/

Alnylam Announces Partnership with Roche to Co-Develop and Co-Commercialize Zilebesiran

CAMBRIDGE, Mass.--(BUSINESS WIRE)-July 24, 2023-Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced it has entered into a strategic agreement with Roche to develop and commercialize zilebesiran, Alnylam's investigational RNAi therapeutic for the treatment of hypertension, which is currently in Phase 2 of development. The partnership allows for a bold development plan with the goal of disrupting the hypertension treatment paradigm globally while advancing Alnylam's P5x25 strategy.

Roche provides Alnylam the benefits of an outstanding partner with a global footprint and a proven track record of developing and commercializing novel therapies in complex markets. Roche has a proven history of innovating and commercializing medicines building upon their extensive global footprint which may potentially enable zilebesiran to reach more patients with hypertension, a disease that affects more than 1.2 billion patients globally.

Under the terms of the agreement, Alnylam will receive an upfront cash payment of $310 million and is eligible to receive additional substantial near-term payments, including development milestone payments over the next few years, as well as regulatory and sales milestones, for a potential deal value of up to $2.8 billion. In addition, Alnylam is entitled to an equal profit share in the U.S., where Alnylam and Roche will co-commercialize zilebesiran. Roche obtained the exclusive right to commercialize zilebesiran outside the U.S. in exchange for low double digit royalties on net sales of zilebesiran outside of the U.S. Alnylam believes that this partnership will allow the companies to pursue a joint development plan and commercialization approach that has the potential to unlock the full value of zilebesiran.

This transactions makes complete sense for Alnylam which otherwise lacks commercial infrastructure in primary care.

This deal marks Roche's re-entry into cardiometabolic disease.

Source: https://www.businesswire.com/news/home/20230723790893/en/Alnylam-Announces-Partnership-with-Roche-to-Co-Develop-and-Co-Commercialize-Zilebesiran-an-Investigational-RNAi-Therapeutic-for-the-Treatment-of-Hypertension-in-Patients-with-High-Cardiovascular-Risk

mRNA Vaccine for Malaria Showing High Promise

mRNA vaccine against malaria tailored for liver-resident memory T cells

Ganley et.al., Ferrier Research Institute, University of Wellington and Maurice Wilkins Centre for Molecular Biodiscovery, Auckland, New Zealand, *Nature Immunology*, July 20, 2023

Malaria is caused by *Plasmodium* species transmitted by *Anopheles* mosquitoes. Following a mosquito bite, *Plasmodium* sporozoites migrate from skin to liver, where extensive replication occurs, emerging later as merozoites that can infect red blood cells and cause symptoms of disease. As liver tissue-resident memory T cells (Trm cells) have recently been shown to control liver-stage infections, we embarked on a messenger RNA (mRNA)-based vaccine strategy to induce liver Trm cells to prevent malaria. Although a standard mRNA vaccine was unable to generate liver Trm or protect against challenge with *Plasmodium berghei* sporozoites in mice, addition of an agonist that recruits T cell help from type I natural killer T cells under mRNA-vaccination conditions resulted in significant generation of liver Trm cells and effective protection. Moreover, whereas previous exposure of mice to blood-stage infection impaired traditional vaccines based on attenuated sporozoites, mRNA vaccination was unaffected, underlining the potential for such a rational mRNA-based strategy in malaria-endemic regions.

It's nice to see such promise for a "high tech" approach to an important tropical disease.

We hope to see an mRNA player develop a malaria vaccine.

Source: https://www.nature.com/articles/s41590-023-01562-6

Tumor-derived GDF-15 blocks LFA-1 dependent T cell recruitment and suppresses responses to anti-PD-1 treatment

nature communications **July 20, 2023**

Immune checkpoint blockade therapy is beneficial and even curative for some cancer patients. However, the majority don't respond to immune therapy. Across different tumor types, pre-existing T cell infiltrates predict response to checkpoint-based immunotherapy. Based on in vitro pharmacological studies, mouse models and analyses of human melanoma patients, we show that the cytokine GDF-15 impairs LFA-1/β2-integrin-mediated adhesion of T cells to activated endothelial cells, which is a pre-requisite of T cell extravasation. In melanoma patients, GDF-15 serum levels strongly correlate with failure of PD-1-based immune checkpoint blockade therapy. Neutralization of GDF-15 improves both T cell trafficking and therapy efficiency in murine tumor models. Thus GDF-15, beside its known role in cancer-related anorexia and cachexia, emerges as a regulator of T cell extravasation into the tumor microenvironment, which provides an even stronger rationale for therapeutic anti-GDF-15 antibody development.

GDF-15 is a cellular stress hormone that plays many roles. This very interesting article out last week suggests that it can suppress T-cell responses to tumors.

Source: https://www.nature.com/articles/s41467-023-39817-3

CatalYm's Anti-GDF-15 Antibody Showing Signs of Anti-Tumor Activity

Munich, Germany, June 5, 2023 – CatalYm today announced first Phase 2a data from its ongoing GDFather-2 trial (**GDF**-15 **A**ntibody-media**T**ed **H**uman **E**ffector Cell **R**elocation Phase 2) (NCT04725474) at the American Society of Clinical Oncology (ASCO) Annual Meeting 2023 in Chicago, Illinois. The early data presented during today's oral "Developmental Therapeutics-Immunotherapy" session revealed lasting and confirmed responses in several solid tumor types investigated following treatment with visugromab and the anti-PD-1 inhibitor nivolumab. In addition, the combination continues to demonstrate a good safety and tolerability profile across all cohorts. CatalYm's lead candidate, visugromab, is a humanized, monoclonal antibody designed to neutralize the tumor-produced Growth Differentiation Factor-15 (GDF-15), a central regulator of tumor resistance development.

"These early data from our Phase 2a cohorts corroborate the encouraging anti-tumor-response we have seen in the Phase 1 study and further elucidate the considerable therapeutic potential of visugromab in very advanced and anti-PD1/PD-L1 relapsed/refractory solid tumor patient populations. They also confirm and further refine our scientifically guided indication selection to identify the solid tumor patients that would most benefit from a GDF-15 modulating approach," said **Prof. Dr. Eugen Leo, Chief Medical Officer at CatalYm**.

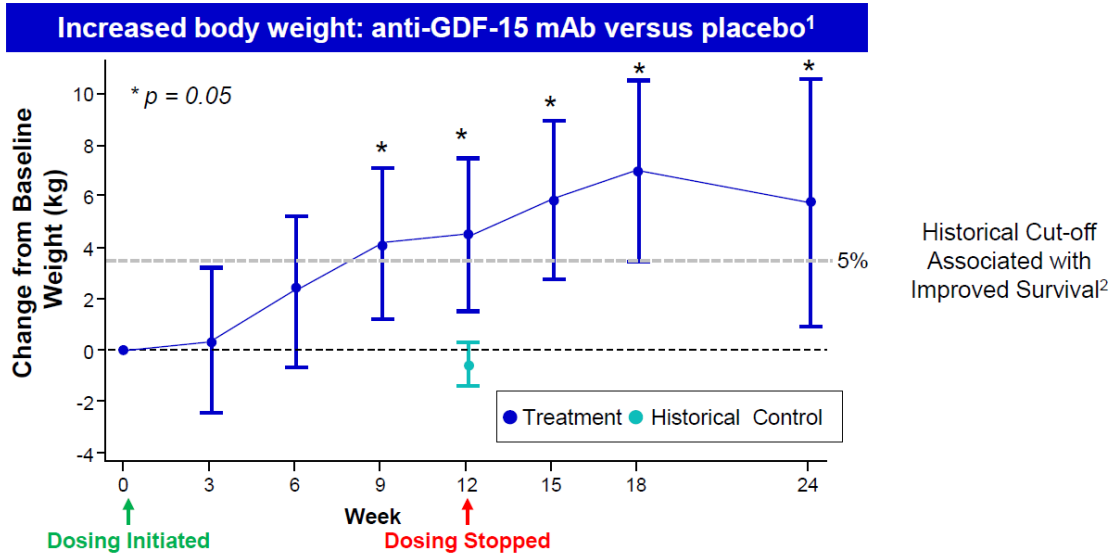
The presentation at ASCO by International Coordinating Investigator Prof. Dr. Ignacio Melero Bermejo, MD, Co-Director of Immunology and Immunotherapy (CIMA) at the Universidad de Navarra, Pamplona/Spain, builds on the further matured Phase 1 trial data announced in September 2022 which showed a significant clinical benefit in last line tumor patients that were anti-PD1/-L1 relapsed or refractory with an overall response rate of 17% in an advanced-stage mixed tumor population (RECIST, all responses confirmed). The Phase 2a study cohorts were selected based on a translational research program and include several major solid tumor types identified in Catalym's translation research program as potentially being GDF-15 influenced.

Source: https://www.catalym.com/catalym-announces-initial-data-from-ongoing-phase-2a-trial-evaluating-gdf-15-targeting-antibody-visugromab-in-combination-with-nivolumab-at-asco-2023/

Pfizer's Anti-GDF-15 Antibody, Ponsegromab, Displays Impressive Weight Gain in Cancer Cachexia

Anti-GDF-15 mAb: Ph 1b (Preliminary Data) in Cancer Cachexia

Significant Increases in Body Weight Demonstrate Target Mediated Efficacy



- **Suppressed circulating GDF-15 levels in cancer cachexia patients** to below the level observed in healthy subjects
  - Suppression was associated with increases in **body weight**
  - Treatment was **well tolerated** and was administered **on top of standard of care** anti-tumor therapy in patients with cancer

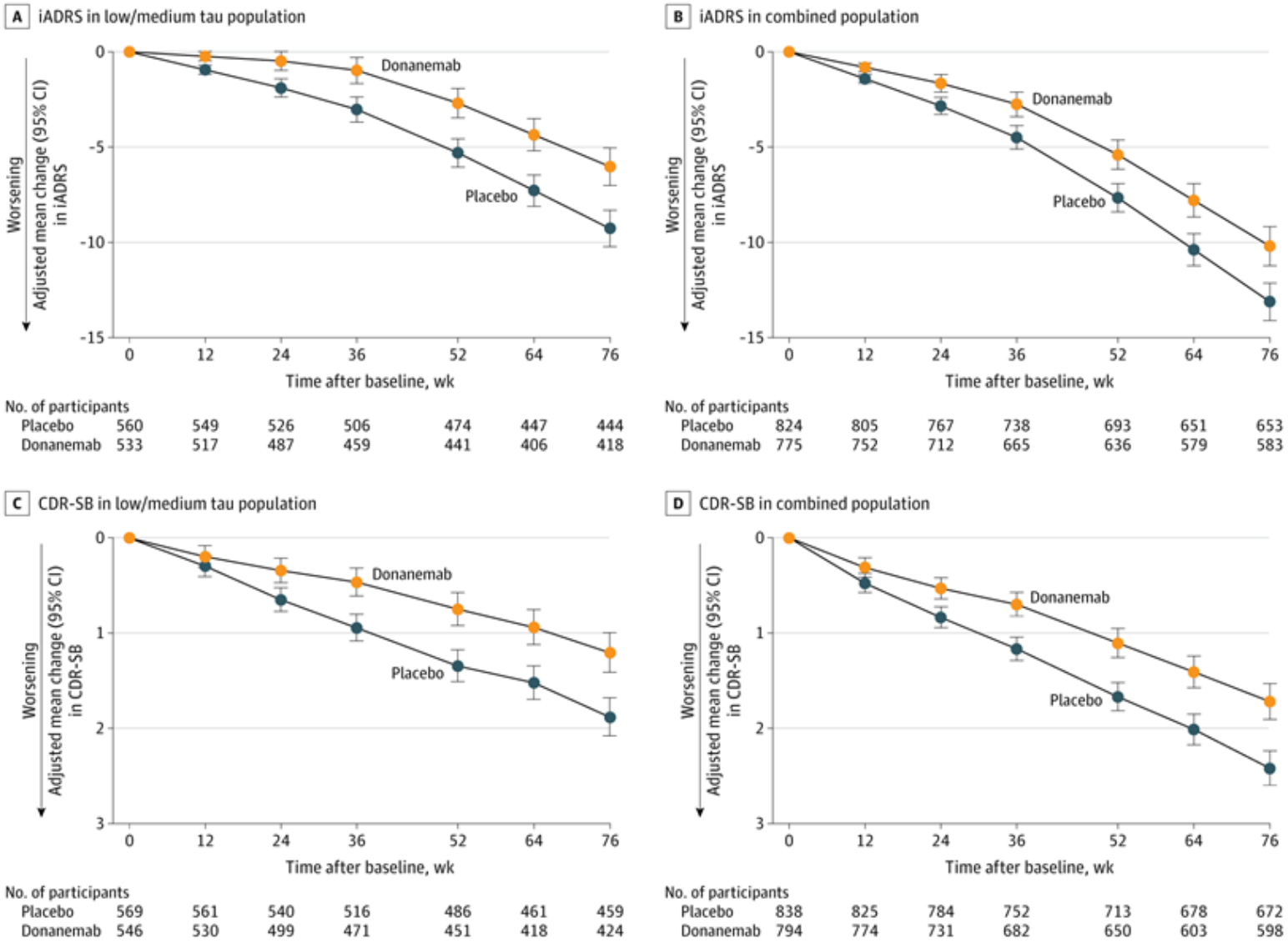
1. Data from C3651009 study. Patients with NSCLC, colorectal cancer or pancreatic cancer diagnosed with cachexia by Fearon criteria and with GDF-15 > 1.5 ng/mL at baseline. Ponsegromab 200 mg administered at week 1, 3, 6, 9 and 12; Placebo comparator was derived from a meta-analysis of data from cancer cachexia studies in the literature, Three Pfizer oncology studies (placebo group) and Real World Data in the Optum database to create the modeled placebo response of -0.6 kg at week 12. Results show means (+/- 90% confidence intervals). 2. Annals of Oncology 27: 1612 – 1619, 2016; mAb: Monoclonal Antibody

Alzheimer’s Data Highlights / AAIC

MRI data for Alzheimer’s Patients. Source: Getty Images

Eli Lilly Data Donanemab Data at AAIC Impressive

In the low/medium tau population, LSM change from baseline in the iADRS score at 76 weeks was −6.02 (95% CI, −7.01 to −5.03) in the donanemab group and −9.27 (95% CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62]; *P* < .001), representing a 35.1% (95% CI, 19.90%-50.23%) slowing of disease progression



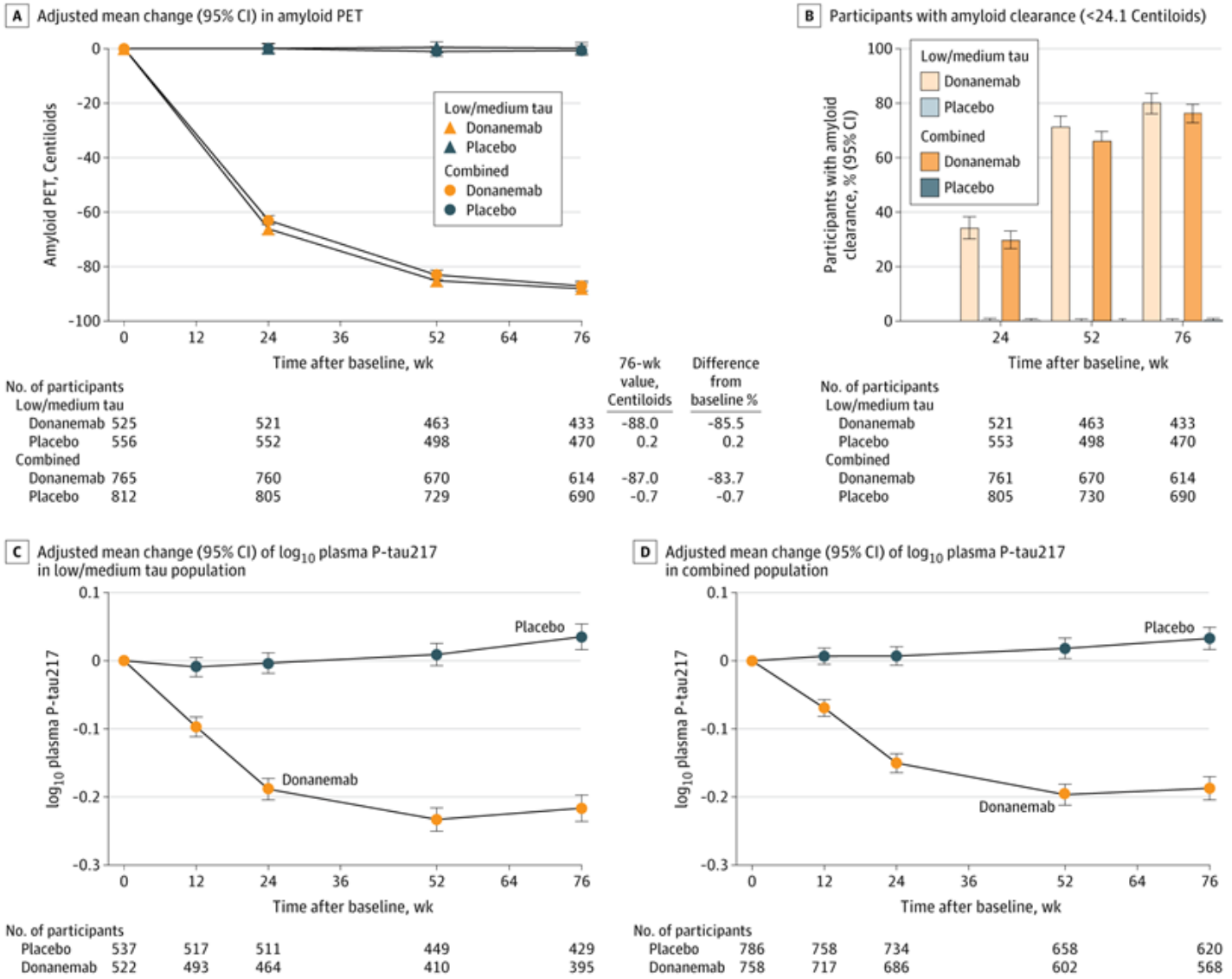
A, 35.1% slowing (95% CI, 19.90%-50.23%) of clinical progression. B, 22.3% slowing (95% CI, 11.38%-33.15%) of clinical progression. C, 36.0% slowing (95% CI, 20.76%-51.15%) of clinical progression. D, 28.9% slowing (95% CI, 18.41%-39.44%) of clinical progression. iADRS data were analyzed using the natural cubic spline model with 2 degrees of freedom (NCS2) and CDR-SB data were analyzed with mixed models for repeated measures (MMRM). For MMRM analyses, 95% CIs for least-squares mean changes were calculated with the normal approximation method. For the Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living, 13-item cognitive subscale of the Alzheimer Disease Assessment Scale, and CDR-SB clinical assessments analyzed with NCS2, see eFigure 1 (low/medium tau population) and eFigure 2 (combined population) in Supplement 3 and Table 2. For all clinical assessments analyzed with MMRM, see eFigure 3 (low/medium tau population) and 4 (combined population) in Supplement 3 and Table 2. *P* < .001 for all 76 week time points.

Source: https://jamanetwork.com/journals/jama/fullarticle/2807533

Donanemab Delivers Massive Reductions in Tau

At 76 weeks, brain amyloid plaque level decreased by 88.0 Centiloids (95% CI, −90.20 to −85.87) with donanemab treatment and increased by 0.2 Centiloids (95% CI, −1.91 to 2.26) in the placebo group in the low/medium tau population; in the combined population, amyloid plaque level decreased by 87.0 Centiloids (95% CI, −88.90 to −85.17) with donanemab treatment and decreased by 0.67 Centiloids (95% CI, −2.45 to 1.11) in the placebo group (Figure 3A). The percentages of donanemab-treated participants in the low/medium tau population who reached amyloid clearance were 34.2% (95% CI, 30.22%-38.34%) at 24 weeks and 80.1% (95% CI, 76.12%-83.62%) at 76 weeks compared with 0.2% (95% CI, 0.03%-1.02%) at 24 weeks and 0% (95% CI, 0.00%-0.81%) at 76 weeks of placebo-treated participants.

Source: https://jamanetwork.com/journals/jama/fullarticle/2807533



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Donanemab Shows Imbalance of ARIA

The incidence of death was 1.9% in the donanemab group and 1.1% in the placebo group, while the incidence of serious adverse events was 17.4% in the donanemab group and 15.8% in the placebo group (Table 3). In the donanemab group, 3 participants with serious amyloid-related imaging abnormalities subsequently died (2 APOE ε4 heterozygous carriers and one noncarrier; none were prescribed anticoagulant or anti-platelet medications; one resumed treatment after resolution of severe amyloid-related imaging abnormalities edema/effusion that was accompanied by severe amyloid-related imaging abnormalities microhemorrhages and hemosiderin deposits and one had superficial siderosis at baseline). Treatment-emergent adverse events were reported by 759 of 853 participants (89.0%) receiving donanemab and 718 of 874 participants (82.2%) receiving placebo. Treatment discontinuation due to adverse events was reported in 112 participants receiving donanemab and 38 participants receiving placebo. The most common adverse events that led to treatment discontinuation were infusion-related reactions, either amyloid-related imaging abnormalities edema/effusion or microhemorrhages and hemosiderin deposits, and hypersensitivity.

Table 3. Summary of Adverse Events (AEs) by Treatment Group

Event	Donanemab (n = 853)[a]	Placebo (n = 874)[a]
Overview of AEs, No. (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[f]	759 (89.0)	718 (82.2)
Treatment-emergent AEs ≥5% incidence, No. (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Urinary tract infection	45 (5.3)	59 (6.8)
Diarrhea	43 (5.0)	50 (5.7)
Fatigue	42 (4.9)	45 (5.1)
Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

Source: https://jamanetwork.com/journals/jama/fullarticle/2807533

Impressive Animal Data from Alector TREM-2 Antibody

Alector is looking to complete enrollment this year in the Phase 2 clinical trial of it TREM2 candidate, AL002, in patients with early Alzheimer's disease.

72737

AL002c-mediated Reduction in Amyloid β Pathology is Reflected by Changes in Plasma Alzheimer's Disease Biomarkers in 5xFAD Mice

Brady Burgess, MSc[1]; Adiljan Ibrahim, MSc[1]; Branden Stansley, PhD[1]; Tina Schwabe, PhD[1]*; Shoutang Wang, PhD[2]; Marco Colonna, MD[2]; Ilaria Tassi, PhD[1]

*[1]Alector, Inc., South San Francisco, CA, USA; [2]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO, USA *Current affiliation: Nine Square Therapeutics, Inc., South San Francisco, CA 94080, USA*

Background

Microglia and TREM2 in Alzheimer's Disease (AD)

- Microglia play a key role in modulating the response to AD pathology, including the clearance and remodeling of amyloid plaques[1-4]
- Several lines of evidence identify triggering receptor expressed on myeloid cells-2 (TREM2) as a critical regulator of microglial response in AD
  - Microglia with decreased TREM2 function demonstrate altered transcriptional response to AD pathology in both human[5,6] and preclinical studies[6,7]
  - Individuals carrying the hypomorphic missense R47H variant in the *TREM2* gene are at a greatly increased risk for late-onset AD (LOAD)[8]

Targeting TREM2 With AL002 in AD

- AL002 is a novel humanized monoclonal TREM2-activating immunoglobulin G1 (IgG1) antibody and is currently being evaluated in INVOKE-2, a phase 2 trial in participants with early AD (NCT04592874)
- Previously, 5xFAD mice treated with AL002c, a variant of AL002, were shown to have an altered composition of amyloid plaques and a reduced number of dystrophic neurons[9]
- Notably, 5xFAD mice treated with AL002c exhibited reduced neurotoxic filamentous plaque despite no change in total methoxy-X04–positive plaque area or insoluble hippocampal amyloid-beta (Aβ) 42 or Aβ40, consistent with a beneficial remodeling of amyloid plaque by microglia[9]

Fluid Biomarkers of AD

- INVOKE-2 will assess exploratory biomarker endpoints in plasma and cerebrospinal fluid (CSF) to characterize the activity of AL002 in the brain and treatment effects on AD pathology
- Aβ peptides
  - Aβ peptides in plasma or CSF are established biomarkers of amyloid burden in the brain[10]
  - Recent clinical trials with amyloid-lowering therapies[11,12] observe that increases in Aβ42[11] or the Aβ42/40 ratio[13] correlate with the extent of amyloid clearance as measured by amyloid positron emission tomography (PET)
  - Despite the observed correlation between Aβ42/40 and amyloid clearance, it is unknown whether plasma Aβ peptides are an informative marker of amyloid plaque remodeling
- Soluble tau
  - Total tau (t-tau) protein is elevated in AD biofluids, correlates with the rate of cognitive decline, and is believed to reflect the intensity of neuronal degeneration in AD[14,15]
  - Biomarkers of neurodegeneration are hypothesized to reflect a cellular process proximal to cognitive decline and are an important complement to earlier markers of the amyloid cascade, including amyloid pathology

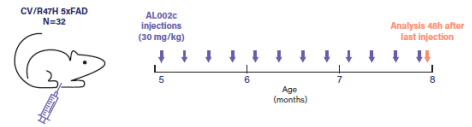
Research Questions

- We sought to establish whether biomarkers of amyloid pathology (Aβ42/40 ratio) or neurodegeneration (t-tau) were sensitive to AL002c treatment effects in 5xFAD mice. Specifically:
  1. Is the plasma Aβ42/40 ratio sensitive to AL002c-induced changes in amyloid plaques in 5xFAD mice, despite no change in total amyloid burden?
  2. Is t-tau an informative biomarker of AL002c-mediated neuroprotection in the 5xFAD model?

Methods

- As described previously[16] CV-KO-5xFAD and R47H-KO-5xFAD mice were generated by introducing either common variant (CV) or R47H human *TREM2* (*hTREM2*) into mouse *Trem2* (*mTrem2*)–deficient mice and crossing them with the 5xFAD mouse model of AD, in which amyloid deposition begins at 2 months[17]
- Five-month-old CV-KO-5xFAD and R47H-KO-5xFAD mice (N=32, n=6-13 per group) received weekly intraperitoneal injections of 30-mg/kg AL002c or a control mouse IgG1 for 12 weeks and were sacrificed 48 hours after the last injection (**Figure 1**)
- Levels of plasma Aβ42, Aβ40, and t-tau were quantified using the Simoa® Neurology 3-Plex A Advantage Kit (Quanterix)
- Group differences in Aβ42/40 ratios were analyzed using Student's t-tests
- Mann Whitney U tests were used to analyze plasma t-tau data
- All statistical tests were conducted using GraphPad Prism
- Significance level was set to 0.05

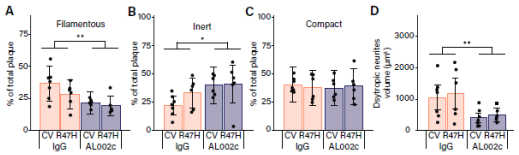
Figure 1. Timeline of AL002c Treatment in CV/R47H 5xFAD Mice



Results

- Wang et al previously showed that, in 5xFAD mice, AL002c treatment reduced the proportion of neurotoxic filamentous Aβ plaques and increased the proportion of inert plaques (**Figure 2A-B**), while compact plaque area (**Figure 2C**) and total brain Aβ42 and Aβ40 levels remained constant[9]
- AL002c-treated mice also exhibited reduced neurite dystrophy (**Figure 2D**) and reversal of a behavioral phenotype observed in 5xFAD mice, consistent with the reduction in neurotoxic pathology[9]

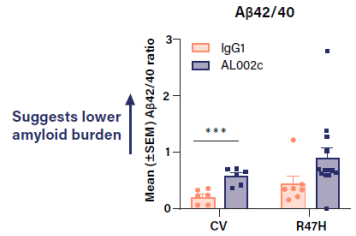
Figure 2. AL002c Shifts Composition of Aβ Plaques and Reduces Neurite Dystrophy



Data are presented as mean ± SEM. *, $p < 0.05$; **, $p < 0.01$ by two-way ANOVA.

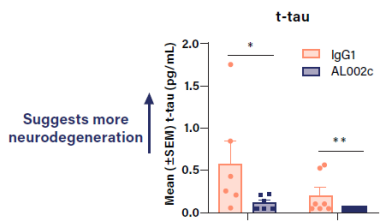
- Here, we show that AL002c-treated CV-5xFAD mice had a higher plasma Aβ42/40 ratio compared with IgG1-treated CV-5xFAD mice ($p < 0.001$; **Figure 3**), while this difference did not achieve significance for R47H-5xFAD mice ($p = 0.056$)
- Pooled AL002c-treated mice had a higher plasma Aβ42/40 ratio compared with IgG1-treated mice (pooled CV and R47H-5xFAD $p < 0.01$)
- AL002c-treated mice exhibited lower plasma t-tau compared with their respective control-treated mice (**Figure 4**; CV-5xFAD $p < 0.05$; R47H-5xFAD $p < 0.01$; pooled CV and R47H-5xFAD $p < 0.001$)
- No differences were observed between R47H and CV genotypes in plasma Aβ42/40 ratio or t-tau

Figure 3. AL002c Treatment Increases Plasma Aβ42/40 Ratio



Note: The dilution-adjusted limit of detection (LOD) was 0.98 pg/mL for Aβ40 and 0.225 pg/mL for Aβ42. An Aβ42/40 ratio could not be calculated for 1 mouse for which Aβ40 data were unavailable: CV-KO-5xFAD, AL002c, n=6; CV-KO-5xFAD, IgG1, n=6; R47H-KO-5xFAD, AL002c, n=12; R47H-KO-5xFAD, IgG1, n=7. Each symbol represents data from 1 mouse. ***, $p < 0.001$

Figure 4. AL002c Decreases Plasma Total Tau Levels



Note: The dilution-adjusted LOD was 0.095 pg/mL. Measurements that were below the LOD were assigned a value of half of the LOD, 0.0475 pg/mL. CV-KO-5xFAD, AL002c, n=6; CV-KO-5xFAD, IgG1, n=6; R47H-KO-5xFAD, AL002c, n=13; R47H-KO-5xFAD, IgG1, n=7. Each symbol represents data from 1 mouse. *, $p < 0.05$; **, $p < 0.01$.

Conclusions

- Treatment with AL002c, a TREM2-agonistic antibody, resulted in an increase in plasma Aβ42/40 ratio and a decrease in plasma t-tau in 5xFAD mice
- AL002c-induced changes in plasma Aβ42/40 levels suggest that the Aβ42/40 ratio can reflect remodeling of amyloid plaques without a reduction in total methoxy-X04–positive plaque or insoluble Aβ42 or Aβ40 burden in 5xFAD mice
- AL002c-induced changes in plasma t-tau suggest that AL002c improves biomarkers of neurodegeneration in 5xFAD mice, consistent with the decrease in dystrophic neurites seen with AL002c treatment[9]
- These results lend further support to the clinical utility of plasma Aβ42/40 as a marker for the reduction of neurotoxic amyloid plaques and t-tau as a marker of neurodegeneration in clinical trials with AL002
- A phase 2 trial (INVOKE-2; NCT04592874) and long-term extension study (NCT05744401) are ongoing to evaluate the efficacy and safety of AL002 in slowing disease progression in participants with early AD

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Disclosures

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Presented at the Alzheimer's Association International Conference | July 16-20, 2023 | Amsterdam, Netherlands

Source: https://investors.alector.com/static-files/521ca08d-e93e-46b4-bf1c-0eb40d634a01

Other Companies in Alzheimer's Disease Hunt

Evaluate Vantage, Jul 18, 2023

The amyloid-lowering era in Alzheimer's might be only just beginning, but some groups are already trying to improve on existing antibodies. One such company is Acumen, which saw its stock rise 55% yesterday on promising phase 1 data presented at AAIC over the weekend.

Acumen believes that by targeting amyloid-beta oligomers, rather than plaques or protofibrils, it could avoid the Aria-E side effects seen with the likes of Eisai and Biogen's Leqembi and Lilly's donanemab. However, on this point the latest results are far from clear.

The Intercept-AD trial found an Aria-E rate of 10% among 48 patients receiving ACU193, versus none among 14 patients on placebo. This is not all that different from the 13% seen in Leqembi's phase 3 study, Clarity AD, with the caveat that Acumen's trial is small and relatively short. One interesting finding in Intercept-AD was a lack of Aria-E among the six patients who were homozygous for the ApoE4 allele – in trials of other anti-amyloid-beta antibodies, these subjects have been shown to have a greater risk of Aria-E.

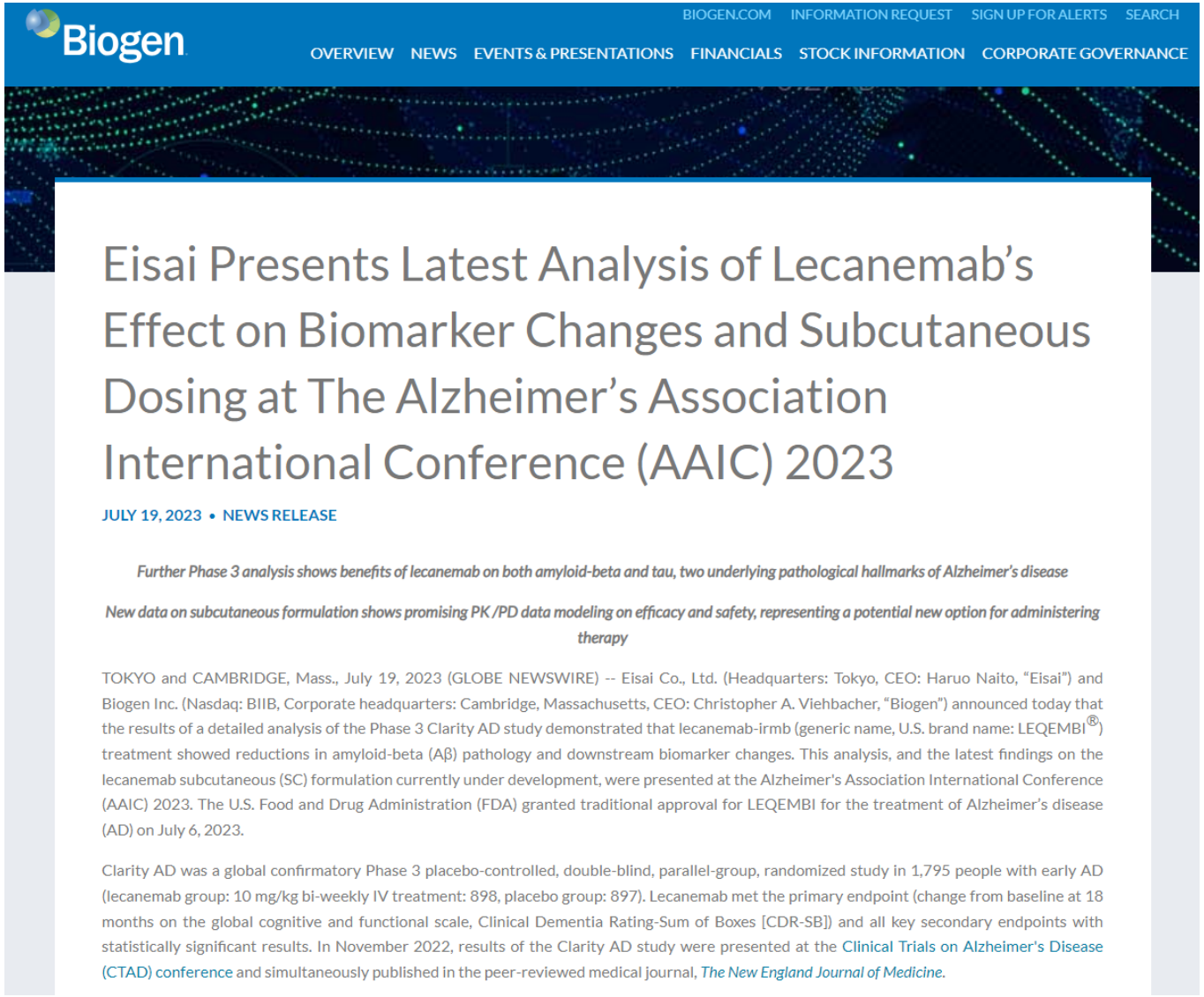
Poster 74181: PRX005, A Novel Anti-MTBR Tau Humanized Monoclonal Antibody: Results from the Single Ascending Dose Portion of a First-in-Human Double-Blind, Placebo-Controlled, Phase 1 Clinical Trial

The results of the Phase 1 clinical trial SAD portion showed that all three dose level cohorts (low, medium, high) of PRX005 were considered generally safe and well tolerated, meeting the Phase 1 clinical trial SAD portion primary objective and supporting evaluation of doses in the MAD portion of the ongoing Phase 1 clinical trial. PRX005 also met key pharmacokinetic (PK) and immunogenicity secondary endpoints. Plasma drug concentrations of PRX005 increased in a dose-proportional manner. As planned, cerebral spinal fluid (CSF) drug levels were measured in the high dose cohort and reached sufficient CSF concentrations to predict pharmacological targeting of MTBR tau in the central nervous system (CNS) (day 29 CSF:plasma ratio=0.2%).

On July 10, 2023, Prothena announced that Bristol Myers Squibb exercised its $55 million option under the global neuroscience research and development collaboration to obtain the exclusive worldwide commercial rights for PRX005. Bristol Myers Squibb will be responsible for the development, manufacturing, and commercialization of PRX005. All program updates, including results from ongoing and any future PRX005 clinical studies, will be reported by Bristol Myers Squibb going forward.

Source: https://www.evaluate.com/vantage/articles/events/conferences/aaic-2023-acumens-new-amyloid-approach-impresses, https://s201.q4cdn.com/351053094/files/doc_news/Prothena-Presents-New-Research-in-the-Treatment-of-Alzheimers-Disease-at-Alzheimers-Association-International-Conference-2023-AAIC-2023.pdf

Impressive Data on Lecanemab Effect Shared Last Week at AAIC



Biogen

BIOGEN.COM INFORMATION REQUEST SIGN UP FOR ALERTS SEARCH

OVERVIEW NEWS EVENTS & PRESENTATIONS FINANCIALS STOCK INFORMATION CORPORATE GOVERNANCE

Eisai Presents Latest Analysis of Lecanemab's Effect on Biomarker Changes and Subcutaneous Dosing at The Alzheimer's Association International Conference (AAIC) 2023

JULY 19, 2023 • NEWS RELEASE

Further Phase 3 analysis shows benefits of lecanemab on both amyloid-beta and tau, two underlying pathological hallmarks of Alzheimer's disease

New data on subcutaneous formulation shows promising PK /PD data modeling on efficacy and safety, representing a potential new option for administering therapy

TOKYO and CAMBRIDGE, Mass., July 19, 2023 (GLOBE NEWSWIRE) -- Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher, "Biogen") announced today that the results of a detailed analysis of the Phase 3 Clarity AD study demonstrated that lecanemab-irmb (generic name, U.S. brand name: LEQEMBI®) treatment showed reductions in amyloid-beta (Aβ) pathology and downstream biomarker changes. This analysis, and the latest findings on the lecanemab subcutaneous (SC) formulation currently under development, were presented at the Alzheimer's Association International Conference (AAIC) 2023. The U.S. Food and Drug Administration (FDA) granted traditional approval for LEQEMBI for the treatment of Alzheimer's disease (AD) on July 6, 2023.

Clarity AD was a global confirmatory Phase 3 placebo-controlled, double-blind, parallel-group, randomized study in 1,795 people with early AD (lecanemab group: 10 mg/kg bi-weekly IV treatment: 898, placebo group: 897). Lecanemab met the primary endpoint (change from baseline at 18 months on the global cognitive and functional scale, Clinical Dementia Rating-Sum of Boxes [CDR-SB]) and all key secondary endpoints with statistically significant results. In November 2022, results of the Clarity AD study were presented at the Clinical Trials on Alzheimer's Disease (CTAD) conference and simultaneously published in the peer-reviewed medical journal, *The New England Journal of Medicine*.

An increase in plasma Aβ42/40 ratio was observed with lecanemab compared to placebo (adjusted mean change from baseline of lecanemab: 0.008, placebo: 0.001, $p<0.0001$). A reduction in plasma p-Tau181 was observed with lecanemab compared to placebo (adjusted mean change from baseline of lecanemab: -0.575 pg/mL, placebo: 0.201 pg/mL, $p<0.0001$). The other biomarkers also improved after treatment with lecanemab. These outcomes suggested lecanemab impacts A/T/N+ biomarkers involved in the AD pathophysiology and exerts biological effects that demonstrate slowing of disease progression.

A Very Long Road

(31 Years from Scientific Discovery to Lecanemab Approval)

1992

Professor Lars Lannelt discovers a mutation that causes Alzheimer's Disease

2001

Lannelt and colleagues publish on the mutation in *Nature Neuroscience*

...shed: 20 August 2001

The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Aβ protofibril formation

Camilla Nilsberth, Anita Westlind-Danielsson, Christopher B. Eckman, Margaret M. Condron, Karin Axelman, Charlotte Forsell, Charlotte Stenh, Johan Luthman, David B. Teplow, Steven G. Younkin, Jan Näslund & Lars Lannfelt

Nature Neuroscience **4**, 887–893 (2001) | Cite this article

7648 Accesses | **890** Citations | **39** Altmetric | Metrics

Abstract

Several pathogenic Alzheimer's disease (AD) mutations have been described, all of which cause increased amyloid β-protein (Aβ) levels. Here we present studies of a pathogenic amyloid precursor protein (APP) mutation, located within the Aβ sequence at codon 693 (E693G), that causes AD in a Swedish family. Carriers of this 'Arctic' mutation showed decreased Aβ42 and Aβ40 levels in plasma. Additionally, low levels of Aβ42 were detected in conditioned media from cells transfected with APP_{E693G}. Fibrillization studies demonstrated no difference in fibrillization rate, but Aβ with the Arctic mutation formed protofibrils at a much higher rate and in larger quantities than wild-type (wt) Aβ. The finding of increased protofibril formation and decreased Aβ plasma levels in the Arctic AD may reflect an alternative pathogenic mechanism for AD involving rapid Aβ protofibril formation leading to accelerated buildup of insoluble Aβ intra- and/or extracellularly.

2003

BioArctic Neuroscience AB was founded by Lars Lannfelt and Pär Gellerfors.

2005

The drug candidate mAb158 (precursor to BAN2401) was isolated at Uppsala University. Collaboration with Eisai starts

2007

Eisai licenses BAN2401 from BioArctic

Eisai Co., Ltd.

4-6-10 Koishikawa, Bunkyo-ku, Tokyo 11...
Phone: 03-3817-5120 Fax: 03-3811...

Eisai is a Human Health Care Corporation striving for innovative solutions in prevention, cure and care for a health and well-being of people worldwide. We combine our talents to understand and meet the needs of patients and their families to enhance the quality of life.

No. 07-47
FOR IMMEDIATE RELEASE
December 4, 2007

Eisai Co., Ltd.

Eisai and BioArctic Neuroscience Enter Exclusive Licensing Agreement with Novel Antibody Treatment for Alzheimer's Disease

The antibody targets the neurotoxin believed to cause Alzheimer's disease

Eisai Co., Ltd. (Headquarters: Tokyo, President and CEO: Haruo Naito) and BioArctic Neuroscience AB (Headquarter: Stockholm, Sweden, CEO: Pär Gellerfors) announced today that on December 3, they signed an exclusive licence agreement for BAN2401, a novel humanized monoclonal antibody, which is being developed as a next-generation therapeutic treatment for Alzheimer's disease. Under the terms of the agreement Eisai obtains the global rights to study, develop, manufacture and market BAN2401 for the treatment of Alzheimer's disease.

BAN2401 is the result of a strategic research alliance between Eisai and BioArctic initiated in 2005 to identify a potential immunotherapy for Alzheimer's disease. The research is based on the Arctic mutation of amyloid beta-peptide (Aβ), discovered by Prof. Lannfelt at Uppsala University, which causes familial Alzheimer's disease.

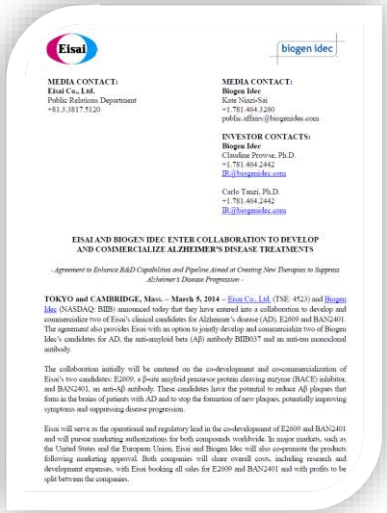
BAN2401 is a humanized monoclonal antibody which selectively recognizes Aβ protofibrils, a form of soluble aggregate of Aβ believed to play a key role in the development of Alzheimer's disease. The antibody is currently in pre-clinical development and Eisai aims to develop a novel treatment for Alzheimer's disease using this antibody.

The licensing agreement for BAN2401, together with the gamma secretase modulator E2012 developed in-house by Eisai, allows the company to pursue parallel approaches to developing next-generation treatments for Alzheimer's disease based on a small molecule compound and antibody therapy.

...ner in Alzheimer's disease treatment, having discovered and developed Aricept® ...drochloride), Eisai aims to accelerate the development of a new generation of ...heimer's disease through in-house activities and alliances with outside

2014

Eisai Collaborates w/Biogen



Eisai

biogen idec

MEDIA CONTACT:
Eisai Co., Ltd.
Public Relations Department
+81.3.3817.5120

MEDIA CONTACT:
Biogen Idec
Kate Nazzi-Sai
+1.781.464.3260
public.affairs@biogenidec.com

INVESTOR CONTACTS:
Biogen Idec
Claudine Prowse, Ph.D.
+1.781.464.2442
IR@biogenidec.com

Carlo Tanzi, Ph.D.
+1.781.464.2442
IR@biogenidec.com

EISAI AND BIOGEN IDEC ENTER COLLABORATION TO DEVELOP AND COMMERCIALIZE ALZHEIMER'S DISEASE TREATMENTS

- Agreement to Enhance R&D Capabilities and Pipeline Aimed at Creating New Therapies to Suppress Alzheimer's Disease Progression -

TOKYO and CAMBRIDGE, Mass. – March 5, 2014 – Eisai Co., Ltd. (TSE: 4523) and Biogen Idec (NASDAQ: BIIB) announced today that they have entered into a collaboration to develop and commercialize two of Eisai's clinical candidates for Alzheimer's disease (AD), E2609 and BAN2401. The agreement also provides Eisai with an option to jointly develop and commercialize two of Biogen Idec's candidates for AD, the anti-amyloid beta (Aβ) antibody BIIB037 and an anti-tau monoclonal antibody.

The collaboration initially will be centered on the co-development and co-commercialization of Eisai's two candidates: E2609, a β-site amyloid precursor protein cleaving enzyme (BACE) inhibitor, and BAN2401, an anti-Aβ antibody. These candidates have the potential to reduce Aβ plaques that form in the brains of patients with AD and to stop the formation of new plaques, potentially improving symptoms and suppressing disease progression.

Eisai will serve as the operational and regulatory lead in the co-development of E2609 and BAN2401 and will pursue marketing authorizations for both compounds worldwide. In major markets, such as the United States and the European Union, Eisai and Biogen Idec will also co-promote the products, following marketing approval. Both companies will share overall costs, including research and development expenses, with Eisai booking all sales for E2609 and BAN2401 and with profits to be split between the companies.

2018

Positive Phase 2b data

2023

FDA approves the drug

FDA NEWS RELEASE

FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval

Action Follows Confirmatory Trial to Verify Clinical Benefit

For Immediate Release: July 06, 2023

Español

Today, the U.S. Food and Drug Administration converted Leqembi (lecanemab-irmb), indicated to treat adult patients with Alzheimer's Disease, to traditional approval following a determination that a confirmatory trial verified clinical benefit. Leqembi is the first amyloid beta-directed antibody to be converted from an accelerated approval to a traditional approval for the treatment of Alzheimer's disease. The drug works by reducing amyloid plaques that form in the brain, a defining pathophysiological feature of the disease.

Leqembi was approved in January under the Accelerated Approval pathway. This pathway allows the FDA to approve drugs for serious conditions where there is an unmet medical need, based on clinical data demonstrating the drug's effect on a surrogate endpoint—in the case of Leqembi, reducing amyloid plaques in the brain—that is reasonably likely to predict a clinical benefit to patients. As a postmarketing requirement of the accelerated approval, the FDA required the applicant to conduct a clinical trial, often referred to as a confirmatory study, to verify the anticipated clinical benefit of Leqembi. Efficacy of Leqembi was evaluated using the results of Study 301 (CLARITY AD), a Phase 3 randomized, controlled clinical trial.

"Today's action is the first verification that a drug targeting the underlying disease process of Alzheimer's disease has shown clinical benefit in this devastating disease," said Teresa Buracchio, acting director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "This confirmatory study verified that it is a safe and effective treatment for patients with Alzheimer's disease."

Eisai's Long-Term Commitment to AD and Executive Tenure

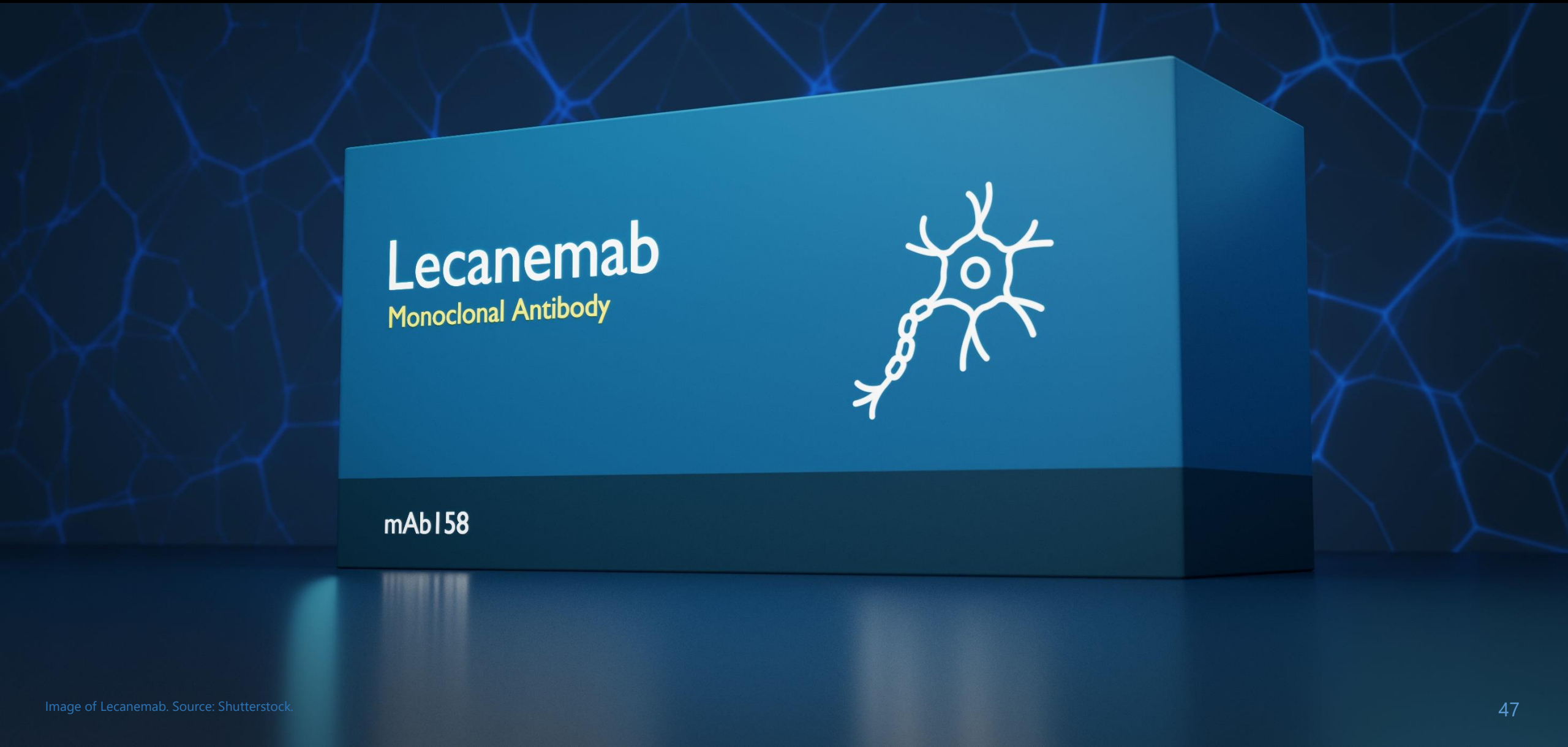


Image of Lecanemab. Source: Shutterstock.

Haruo Naito
CEO, Eisai

Drove the gutsy decisions that led to the approval of LEQEMBI®, for Alzheimer's Disease

The achievement of a lifetime.

Of course, Mr. Naito shares credit for Leqembi's approval with many others, particularly, Dr. Lannelt. But Naito-San drove Eisai relentlessly over decades to develop a drug that would work for Alzheimer's patients. This mission to outsiders may have looked foolish but he was not deterred. Today, Eisai continues to "bet the company" on getting a successful launch for Leqembi. Looking back, Naito-San's determination has to be seen as one of the most impressive human stories of an executive in the history of the pharmaceutical industry.

This achievement may have involved a little luck, but we hope to convey in the slides that follow, Eisai's long-term strategic intent to be successful in neuroscience. Eisai's behavior was rational but driven by an extraordinary desire to make a difference for patients.

Source: Getty Images, Photograph taken in 2022.

In 2004 to 2006 Period Eisai Ramps up R&D, Globalizes R&D Platform and Focuses on Neuro and Oncology

Inaugural Year of Dramatic Leap Plan: FY2006

- **Current Status of Pipeline**
- **Improve Capabilities to Create New Drugs and Reinforce R&D Management**
- **Promote Transformation Strategy**
- **Redefining Globalization**
- **Enhancing Return to Shareholders**

DRAMATIC LEAP PLAN 2011

Improve Capabilities to Create New Drugs and Reinforce R&D Management

4. Therapeutic areas of Focus

Integrative Neuroscience, Integrative Oncology

5. Strive to satisfy unmet medical needs

E7389, E2007, E5564, AS-3201, E5555, E2012, E7974

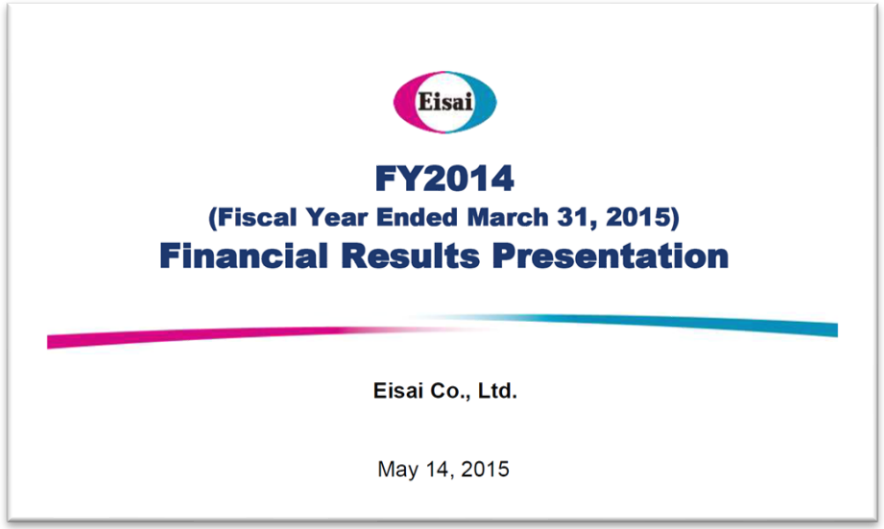
6. Improve value of global products

New indications and new formulations for *Aricept*®, *AcipHex*®/*Pariet* and *Zonegran*®

7. Strengthen project management capabilities

- Eisai R&D Management Co., Ltd. to directly supervise international project teams
- Management with shared goals and unified intention: Decision-making by all directors of research and development, marketing, regulatory and pharmacovigilance

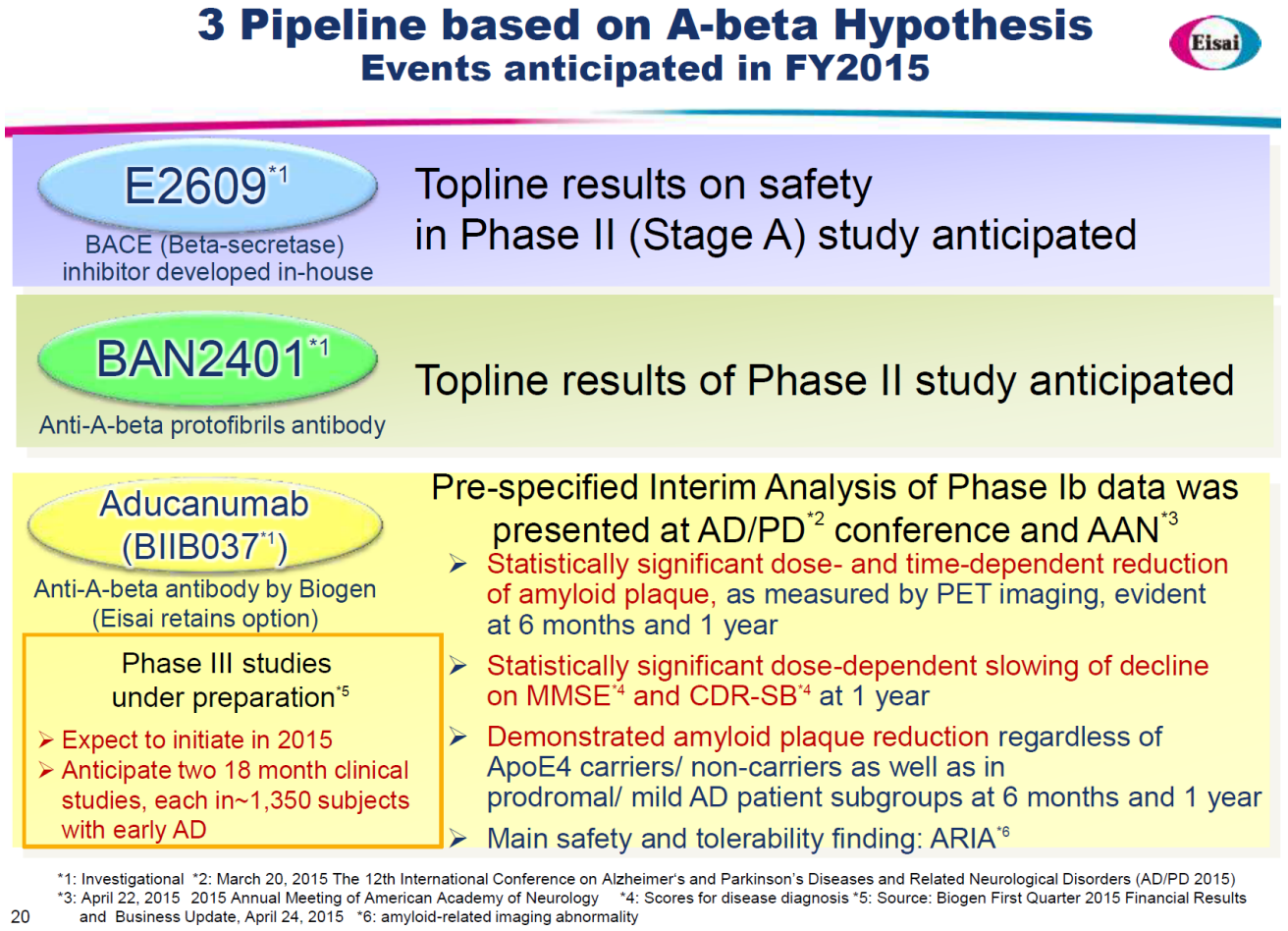
By 2015 Eisai is Highly Focused on Alzheimer's Disease



Eisai Annual Investor Presentation in May 2015

"As a pioneer in the field of dementia treatment, it is our objective to accelerate development of next generation Alzheimer's disease treatments including E2609, a s-site amyloid precursor proteincleaving enzyme (BACE) inhibitor, and BAN2401, an anti-amyloid beta (As) antibody, by way of collaboration with Biogen Idec, Inc., which has world-class strengths in neurodegenerative diseases."

Haruo Naito, Representative Director, Eisai, 2015



By 2023 Eisai Focuses Entire Company on LEQEMBI® Launch

LEQEMBI (lecanemab-irmb)

Toward Value Maximization of LEQEMBI*1

Plan to submit two value maximization programs in FY2023:

Subcutaneous administration (auto-injector formulation): substudy in Clarity AD - OLE*2

Maintenance dosing regimen (once/4 weeks) : substudy in Study 201 - OLE

Pen type auto-injector*3

TERUMO

YPSOMED SELFCARE SOLUTIONS

Full approvals are anticipated globally in FY2023:

The US (Priority Review)	June 9 Advisory Committee	July 6 PDUFA*4 action date
Japan (Priority Review)		Approval anticipated in Q2
EU		Approval anticipated in Q4
China (Priority Review)		Approval anticipated in Q4

*1: Antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic. Collaboration with Biogen. Generic name is lecanemab. *2: Open Label Extension study
*3: Co-development with Terumo Corporation (Auto-injector supplied by Ypsomed) *4: Prescription Drugs User Fee Act

5

LEQEMBI (lecanemab-irmb)

Readiness toward Full Approval in the US

Cognitive function tests	• Developing a different version of Cognigram*1 which enables assessment in a shorter period of time • Utilizing MOCA*2 as an evaluation for cognitive function to diagnose mild cognitive impairment (MCI)
Aβ tests	PET/CSF • Collaborating with diagnostic companies and reference laboratories with the goal of wide-usage by HCPs and reimbursement Blood-based biomarker (BBBM) • Initiated using C_2N Diagnostics' PrecivityAD® as prescreening to achieve diagnostic efficiency • Conduct and evaluate BBBM study for real world use and aim to incorporate BBBM diagnosis into guidelines
IDN*3 Integrated Delivery Network	• Completed clinical presentations with most of the top 40 IDNs • Achieved positive P&T*4 decisions at 8 key IDNs
Infusion centers	• Provided over 600 infusion centers with educational sessions detailing LEQEMBI*5 administration since Accelerated Approval • Working with National Infusion Center Association (NICA) to raise awareness of LEQEMBI for HCPs
Management of ARIA	Education program "Understanding ARIA*6" provides medical resources on ARIA in multiple learning formats Steady progress in raising awareness among HCPs, and this program was accessed over 2,900 times*7 since its launch at the end of January 2023 • On March 17th, first live webinar was conducted by neuroradiologists on ARIA cases detected by MRI • Conducted 19 ARIA MRI Reader sessions at AAN*8

*1: In the United States, "Cogstate Brief Battery" has been developed by Cogstate with the function of providing expert assessment feedback for healthcare professional use and has been approved as a medical device with the name "Cognigram". It is being used by doctors and other healthcare professionals in examination and diagnosis of MCI (Mild Cognitive Impairment) and dementia. Cognigram cognitive test results are not a stand-alone diagnostic. A version in which assessment can be done in a shorter time as a simpler tool to raise awareness of Brain Health is under development. *2: Montreal Cognitive Assessment
*3: Organization that owns and operates a network of several healthcare facilities such as hospitals, care centers, clinics. *4: Pharmacy and Therapeutics
*5: Antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic. Collaboration with Biogen. Generic name is lecanemab.
*6: This program is not specific to LEQEMBI. ARIA: Amyloid-related imaging abnormality *7: as of the end of April 2023 *8: Annual Meeting of American Academy of Neurology held in Boston on April 22 to 27, 2023

7

Eisai annual report (May 2023): "Alzheimer's disease (AD) treatment Leqembi (lecanemab) obtained accelerated approval in the United States in January 2023, and we are expediting efforts to obtain regulatory approval and expand access in other countries around the world. By providing Leqembi as a new treatment option to eligible people living with AD, we are aiming to create social impact, including not only the clinical value of the drug, but also the economic value of improving patients' and caregivers' quality of life (QOL) and productivity, and reducing the financial burden of medical and long-term care. In addition, to contribute to relieving anxieties over health and reducing health disparities for all people living with dementia, we are building an ecosystem with solutions including a one-stop online health platform for dementia in China, and collaboration with other industries and non-profit organizations in Asia."

Comments from Haruo Naito

"The primary focus of health care must always be the patient, the patient's family, and from a general vantage point, the public as a whole."

"I think it is safe to say that the results have proved that the condition will improve by removing the amyloid-beta aggregates. With lecanemab as a beginning, we are feeling increasingly confident that we can develop the next Alzheimer's drugs, one after the other."

"I'm filled with embarrassment and feel sorry that it took that long. Alzheimer's disease is complicated in character, and we've repeatedly failed and learned from mistakes we made. I hope we don't have to take that long to come up with other drugs."

"I have come to understand what kind of environment we must establish in order for long-awaited new drugs, both by patients and doctors, to be accepted in society,"

Source: Eisai web site, Bloomberg, Financial Times

Haruo Naito Part of a Long Family Line

It's impressive to see Haruo Naito with a 35-year stint as CEO. Actually, he has worked at Eisai for 48 years. Interestingly, Toyoji Naito, founder worked at Eisai (and its predecessor company) for 51 years! We wish newly appointed President Koisuke Naito a similarly long and successful tenure.

1966

Yuji Naito Takes President Role from Toyoji Naito

(*from left*) President Yuji Naito, Chairman Toyoji Naito, and Executive Vice President Tatsuo Naito

1988

Haruo Naito Accepts President Role from Yuji Naito

Newly appointed Chairman of the Board Yuji Naito presents two symbolic batons to newly appointed President Haruo Naito in June 10, 1988. The first baton is inscribed with Eisai's performance figures from the previous fiscal year, while the other is left blank for Haruo to inscribe the figures for Eisai's best performance under his tenure and pass on to the next president when he retires.

2023

Koisuke Naito Appointed President by Haruo Naito

Source: Eisai web site

Company History: Toyoji Naito Takes Eisai Predecessor Company (Sakuragaoka Laboratory) into Vitamins in 1933. Founds Eisai in 1938 and Starts in Pharma in 1915

Sakuragaoka Laboratory researchers group photo in 1940

Source: Eisai web site

Nihon Eisai was founded by Toyoji Naito in 1938. The company's story started much earlier – when Toyoji moved to Tokyo in 1915 and started working at Tanabe Motosaburo Store Co., Ltd. (now part of the Mitsubishi Tanabe Pharma Corporation) and begins to develop OTC products. In 1921 the store acquires Japan's first anti-hypertensive drug.

By the 1930's Toyoji was now well known in the industry for his successes in new drug development and marketing strategy, but he remained dissatisfied with how Japan's drug industry at the time remained reliant on imports.

It was with this in mind that Toyoji then established Sakuragaoka Laboratory Co., Ltd. There he ordered the development of vitamin E product *Juvela*, in doing so marking the beginnings of full-scale commercial vitamin E synthesis in Japan. He also visited the pharma industries of Europe and the U.S. at this time.

Comments from Toyoji Naito

"To work capably is the greatest happiness of all."

"Be a demon in the daytime and a Buddha at night."

"Live life to the fullest again after retirement."

An Obvious Comment: Long Executive Tenure Can be a Good Thing

Harvard Business Review, Jul 2013

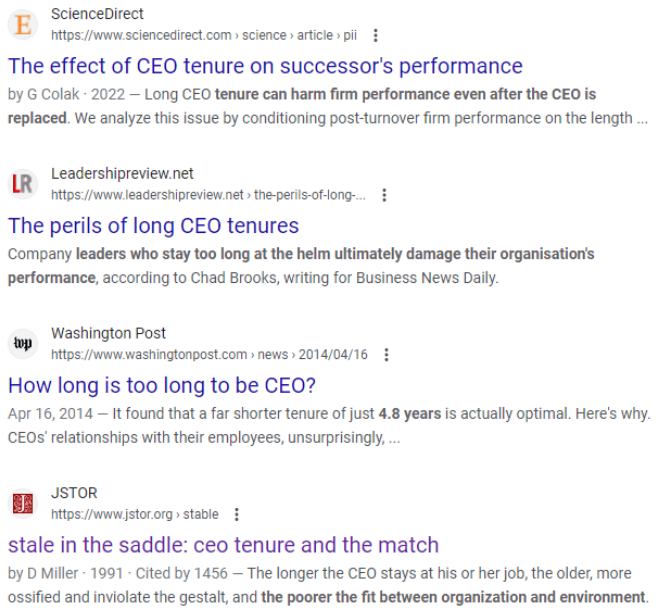
Long CEO Tenure Can Hurt Performance

by Xueming Luo, Vamsi K. Kanuri, and Michelle Andrews

From the Magazine (March 2013)

It's a familiar cycle: A CEO takes office, begins gaining knowledge and experience, and is soon launching initiatives that boost the bottom line. Fast-forward a decade, and the same executive is risk-averse and slow to adapt to change—and the company's performance is on the decline. The pattern is so common that many refer to the "seasons" of a CEO's tenure, analogous to the seasons of the year.

New research examines the causes of this cycle and shows that it's more nuanced than that. We found that CEO tenure affects performance through its impact on two groups of stakeholders—employees and customers—and has different effects on each. The longer a CEO serves, the more the firm-employee dynamic improves. But an extended term strengthens customer ties only for a time, after which the relationship weakens and the company's performance diminishes, no matter how united and committed the workforce is.



It didn't take us a lot of Google searching to find a host of studies and articles that argued that CEO's should not have long tenure. One study shows that the average U.S. CEO tenure is around eight years.* Few companies in the U.S. have the type of dynastic succession approach sometimes seen in China, Europe, Japan and India.

While we are not advocates of widespread executive gerontocracy, it seems obvious that Haruo Naito would have been unlikely to have invested in BAN2401 if he had expected to be in the job for ten years or less. The reality is that pharma projects have incredibly long development timelines, that organizations like Eisai take decades themselves to build and develop and that a single individual's commitment to a vision is important. We have seen countless cases where new leadership brings change in priorities – which are not always good for the company involved.

We suspect that long tenure in the biopharmaceutical industry can be a good thing, on balance. Eisai is far from the only company that has benefitted from the long-term commitment of a visionary leader to organizational development and a pipeline buildout.

Source: https://hbr.org/2013/03/long-ceo-tenure-can-hurt-performance

* https://chiefexecutive.net/banking-and-pharma-sectors-report-high-ceo-turnover__trashed/amp/

Tenure Comparison

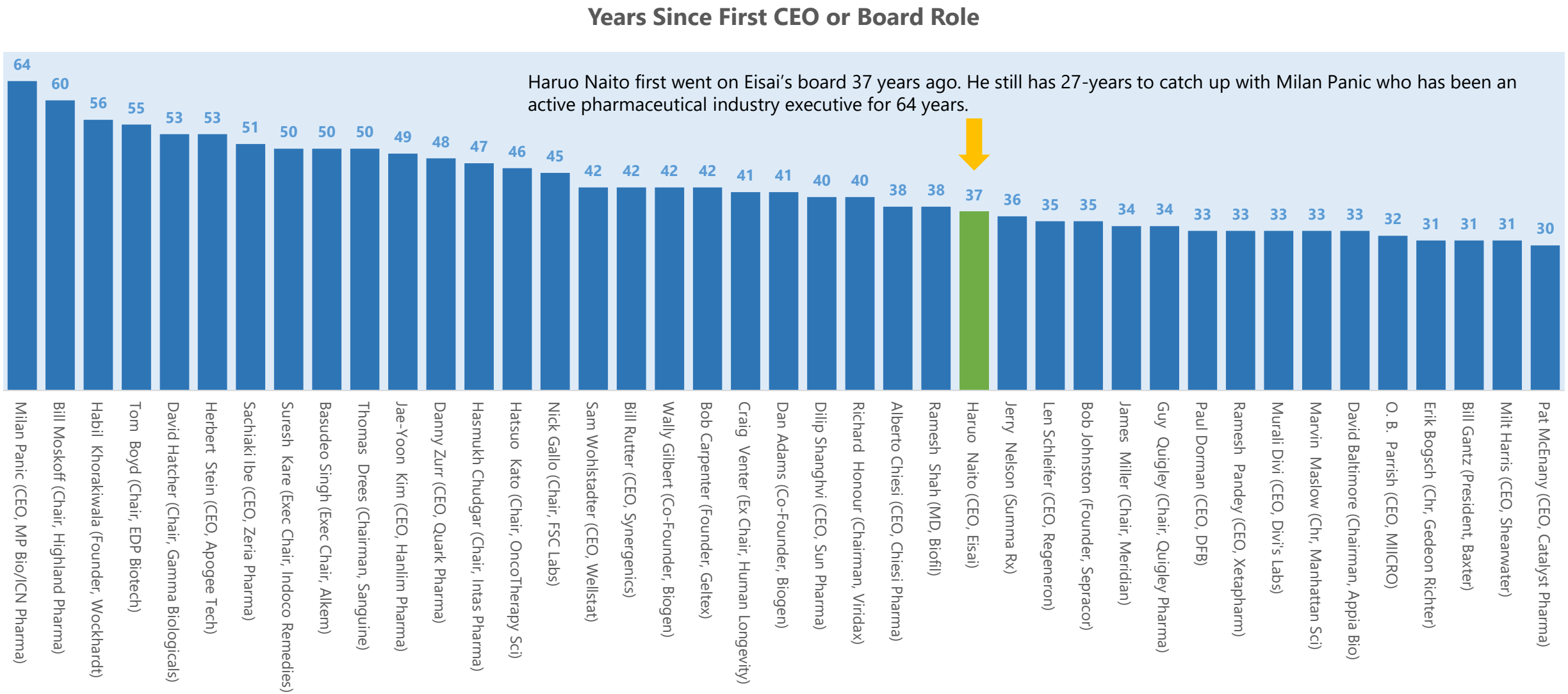
Two 50-year careers for CEO's at Eisai strike us as highly unusual. We thought it would be interesting to collect some data for comparison.

Image of long business journey: Getty Images.

Some Interesting Longevity Benchmarks

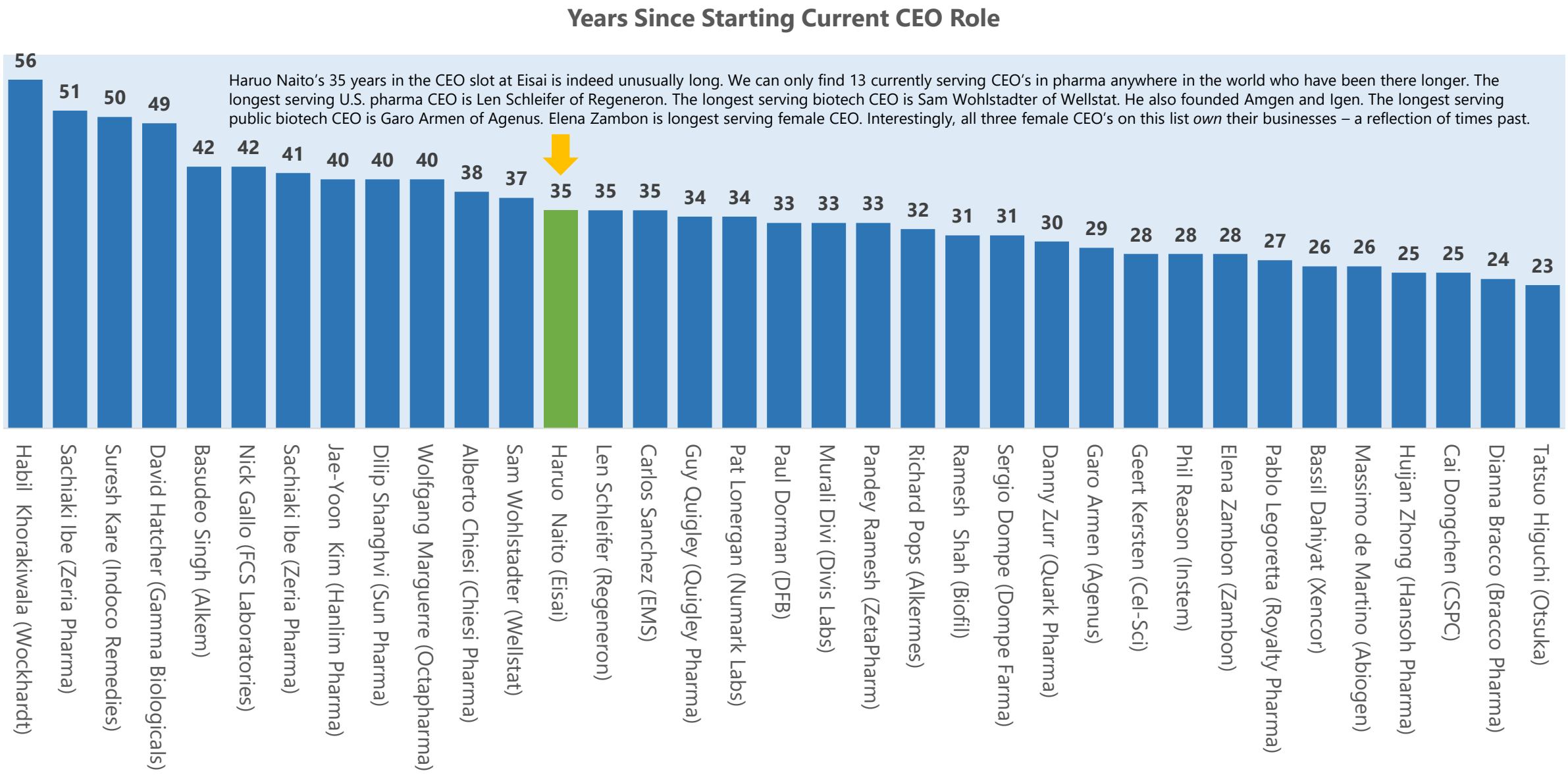
- **David H. Murdock**, owner of Castle & Cooke, has vast business interests and is one of the world's wealthiest persons. He started work in 1943 (80 years ago) and is 100 years old. Mr. Murdock is extremely acquisition and frequently considers business acquisitions. He eats vegetables and fish. Loves pineapple (he founded Dole Foods) and has a keen interest in the pharma / health sector.
- **Warren Buffett** has been CEO of Berkshire Hathaway for 53 years (longest serving CEO in the S&P 500). He's a mere 92-years old. His business partner, Charlie Munger is 99-years old and, like, Mr. Murdock, started work in 1943. Berkshire's value is up 304x since he started.
- **Bill Pollock** of Australia's Drake International has been CEO or Chairman since 1951. That's 72-years in the role. He is apparently the world's longest serving CEO today.
- **Tony Bennett** (died last week) started singing in 1951 and was playing the piano and singing up to July. That's a 72-year career. Compare to Enrico Caruso's 95-year career and Bing Crosby's 86 years.
- **Ron Kruszewski**, our CEO at Stifel, is an absolute youngster, having been in the job for a mere 26 years. He started working in 1980 (53 years ago). Stifel's value is up 35x since he took the job.
- Honorable mention in pharma goes to **Marino Golinelli**. Born in 1920, he founded Biochimici Alfa in 1948. Later, the company became Alfa Wassermann and then - merging with Sigma Tau - Alfasigma, a mid-sized Italian pharma. He oversaw the company for 54 years – longer than Warren Buffett. Mr. Golinelli, sadly, passed away last year at the age of 102. His 100th birthday website is touching.

Longest Tenure Periods in the Life Sciences



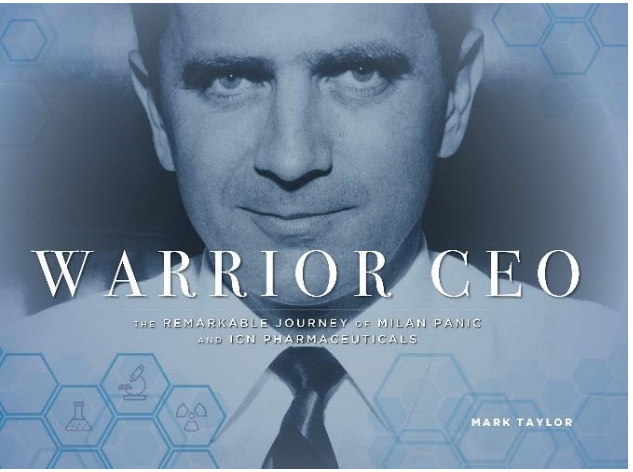
Source: CapitalIQ and Stifel Research

Longest Time in Current CEO Role



Source: CapitalIQ and Stifel Research

Milan Panic: An Extraordinary Pharma Career



Milan Panic built an extraordinary career in pharma chronicled in the book *Warrior CEO* (at right). He grew ICN Pharmaceuticals from a small operation in his garage into a global pharmaceutical corporation listed on the New York Stock Exchange, with over $672 million in annual sales across 90 countries at its peak. ICN was known for Ribavirin and went through significant ups and downs (see right). After retiring from ICN, he spun off an ICN subsidiary and renamed it MP Biomedicals. Today at the age of 93, he controls MP Global Enterprises which has continuity with his original pharma business. Mr. Panic served as the Prime Minister of the Federal Republic of Yugoslavia from 1992 to 1993. During and after his time as Prime Minister, he campaigned for peace and democracy in the Balkan region. Panić was the first US citizen to occupy a high-level political position in a foreign country since Golda Meir. Today, he is a frequent sponsor of California cultural institutions and charities.

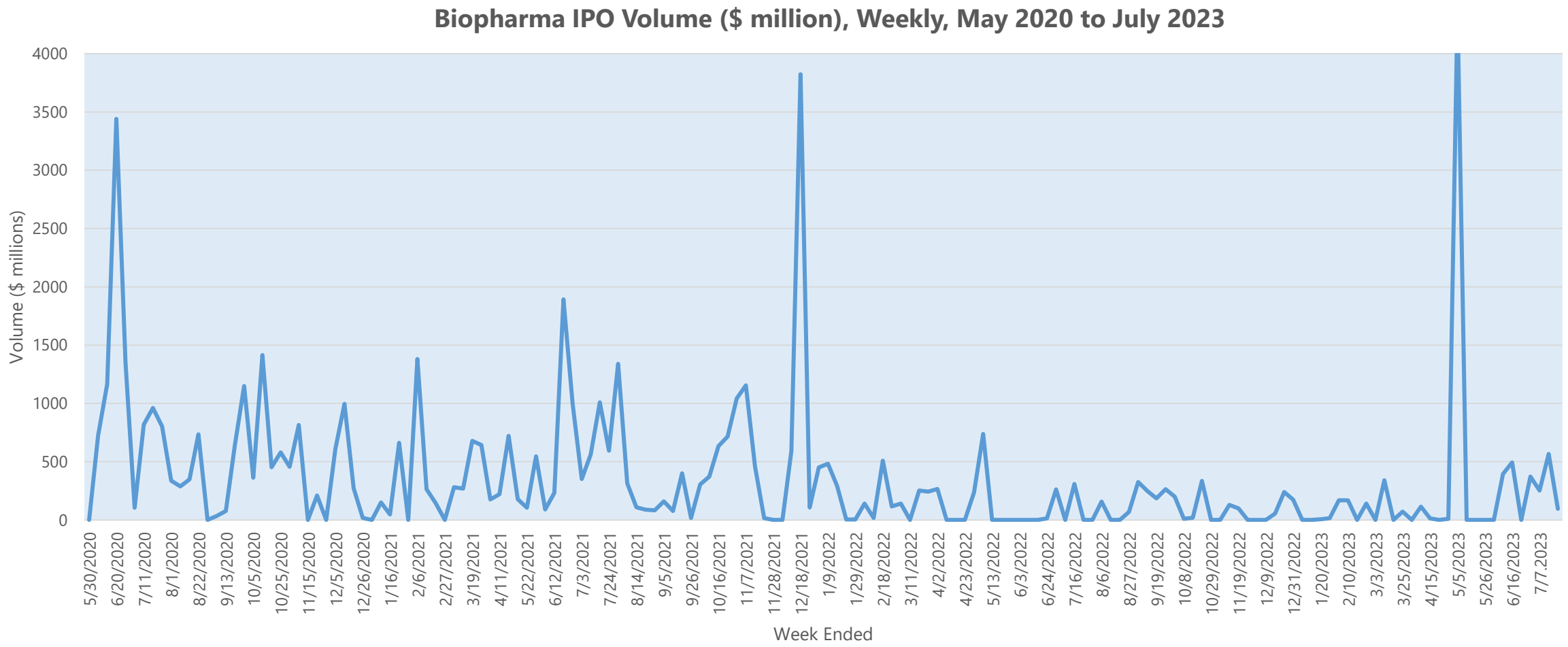
Source: Various, including Wikipedia.

Capital Markets Environment

Medical worker greeting patient. Source: Getty Images.

Turnstone IPO Priced Last Week

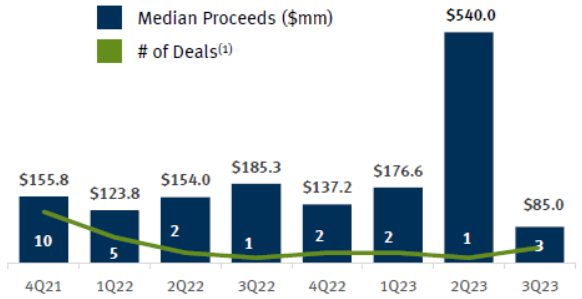
Last week saw Turnstone Bio price its IPO.

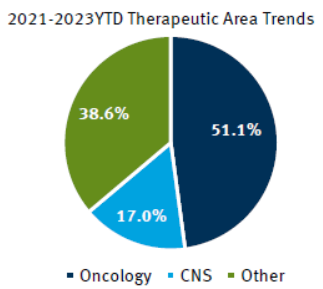


Source: Data from CapitalIQ and Stifel research.

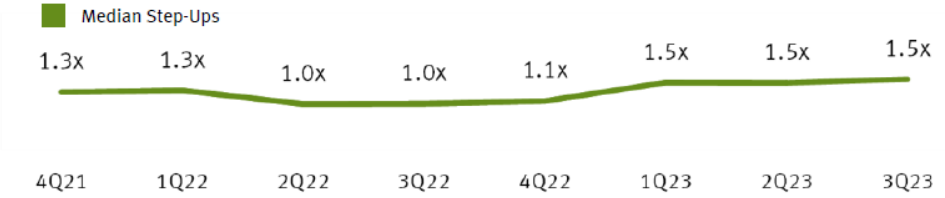
IPO Market Details

Biopharma IPO Proceeds Have Remained Consistent

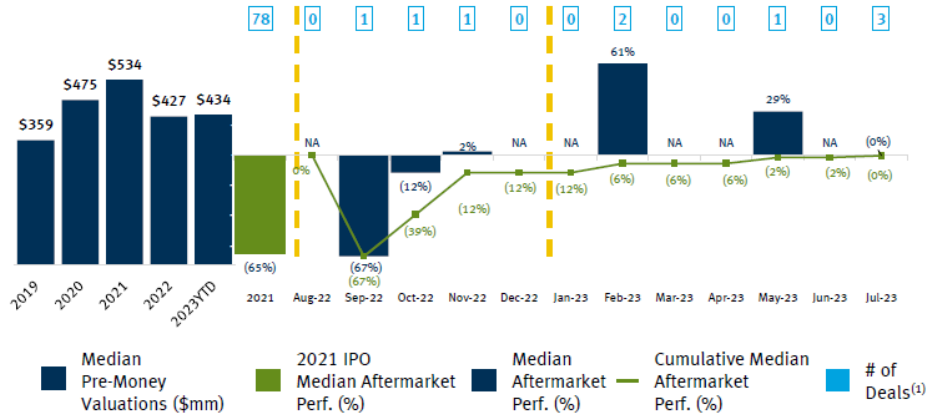




IPO Step-Ups Remain Deal Dependent



Pre-Money Valuations Have Fallen And Performance Has Been Lackluster(2)



30 Most Recent Biotech IPOs

($ in millions)

Issuer	Offer Date	Issuance Amount	Pre-Money Valuation	Pricing vs. Range	Step-Up	Price Change Offer to Day 1	Price Change Offer to Current
Turnstone Biologics Corp.	07/20/23	$80.0	$194.1	Low End	0.5x	(8.3%)	(8.3%)
Sagimet Biosciences Inc.	07/13/23	85.0	301.4	Midpoint	1.5x	(0.3%)	(0.4%)
Apogee Therapeutics, Inc.	07/13/23	300.1	511.1	High End	2.0x	24.9%	20.0%
ACELYRIN, Inc.	05/04/23	540.0	1,221.5	High End	1.5x	30.6%	28.8%
Mineralys Therapeutics, Inc.	02/09/23	192.0	452.8	High End	1.7x	15.3%	(5.6%)
Structure Therapeutics, Inc.	02/02/23	161.1	414.3	High End	1.2x	73.3%	127.2%
Acrivon Therapeutics, Inc.(3)	11/14/22	99.4	183.0	Below	0.9x	33.1%	2.4%
Prime Medicine, Inc.	10/20/22	175.0	1,501.9	Midpoint	1.2x	(9.6%)	(11.7%)
Third Harmonic Bio, Inc.	09/14/22	185.3	496.0	Midpoint	1.0x	15.8%	(67.2%)
PepGen, Inc.	05/05/22	108.0	169.1	Below	0.8x	7.4%	(34.8%)
HilleVax, Inc.	04/28/22	200.0	449.8	Midpoint	1.3x	12.3%	(10.0%)
AN2 Therapeutics, Inc.	03/25/22	69.0	230.7	Midpoint	1.0x	2.7%	(47.9%)
Arcellx, Inc.	02/04/22	123.8	436.7	Low End	1.3x	12.0%	125.7%
Vigil Neuroscience, Inc.	01/07/22	98.0	329.0	Below	1.4x	(9.6%)	(48.4%)
Amylyx Pharmaceuticals, Inc.	01/07/22	190.0	955.8	Midpoint	1.9x	(4.9%)	18.7%
CinCor Pharma, Inc.(4)	01/07/22	193.6	417.9	Midpoint	1.2x	0.0%	62.5%
Vaxxinity Inc	11/11/21	78.0	1,720.2	Below	1.0x	27.3%	(79.1%)
IO Biotech, Inc.(5)	11/04/21	100.1	300.6	Low End	1.0x	11.8%	(86.8%)
Evotec SE	11/03/21	435.0	3,411.2	Below	NA	1.1%	(39.8%)
LianBio	11/01/21	325.0	1,490.0	Midpoint	1.7x	(14.4%)	(86.1%)
Entrada Therapeutics, Inc	10/28/21	181.5	455.3	Midpoint	1.3x	19.8%	(14.7%)
Aura Biosciences Inc	10/28/21	75.6	349.3	Low End	1.3x	5.7%	(15.6%)
Xilio Therapeutics Inc	10/21/21	117.6	339.4	Low End	1.2x	0.0%	(82.2%)
Ventyx Biosciences, Inc.	10/20/21	151.6	690.2	Midpoint	1.3x	31.4%	123.5%
Pyxis Oncology, Inc.	10/07/21	168.0	394.5	High End	1.5x	(17.5%)	(83.9%)
Theseus Pharmaceuticals, Inc.	10/06/21	160.0	500.2	High End	1.1x	16.1%	(77.6%)
Exscientia Plc(6)	09/30/21	464.7	2,146.2	High End	1.9x	23.2%	(62.9%)
DICE Therapeutics, Inc.	09/14/21	204.0	415.2	High End	1.3x	117.0%	174.4%
Tyra Biosciences, Inc.	09/14/21	172.8	515.8	High End	1.5x	62.5%	0.5%
Eliem Therapeutics, Inc.	08/09/21	80.0	263.9	Below	0.8x	27.2%	(78.2%)
Last 30 IPO Summary Statistics:							
Mean		**$183.8**	**$708.6**		**1.3x**	**16.9%**	**(8.6%)**
Median		**$164.6**	**$443.3**		**1.3x**	**12.1%**	**(13.2%)**

Source: Stifel Capital Markets as of July 21, 2023. Amounts raised in concurrent private placements are included as part of the IPO issuance amount. Pre-money equity values at pricing are fully diluted, accounting for options and warrants using the Treasury Stock Method. Excludes IPOs with total proceeds of less than $50.0mm or greater than $1.0bn.
Note: Highlighted IPOs represent Stifel bookrun offerings.
(1) Number of deals includes re-IPOs (companies with a previous foreign listing that list on a U.S. exchange).
(2) Median aftermarket performance represents current performance.

Nasdaq Biotech IPOs in 2023 Trading Well

The average current/offer of the six IPO's that have priced this year is 27%, driven mainly by strong aftermarket performance of Structure Therapeutics, Acelyrin and Apogee. Last week's Turnstone deal has not performed well so far.

Offer Date	Target/Issuer	Amount Raised ($mm)	Issue Price	Price at Offer Date Close	Price Jul 21, 2023	Current / Offer
07/20/2023	Turnstone Biologics	$80	$12.0	$11.0	$11.0	-8.3%
07/13/2023	Sagimet Biosciences	$85	$16.0	$16.0	$15.9	-0.4%
07/13/2023	Apogee Therapeutics	$300	$17.0	$21.2	$20.4	20.0%
05/04/2023	Acelyrin	$540	$18.0	$23.5	$23.2	28.8%
02/14/2023	Mineralys Therapeutics	$192	$16.0	$18.0	$15.1	-5.6%
02/07/2023	Structure Therapeutics	$161	$15.0	$23.3	$34.1	127.2%
Average		$226mm				27.0%
Median		$177mm				9.8%

Source: Data from CapitalIQ and Stifel research. Photo from Getty Images. NASDAQ offerings of $50mm or more included.

Stock Market Gains Help Pave Way for IPO Resurgence in 2023 After Worst Year Since Great Recession

Alex Veiga, Associated Press, July 21, 2023

The rebound in IPOs is being fueled by a resilient stock market rally that has the S&P 500 up about 19% so far this year, a sharp reversal from last year's 19.4% loss.

Another reason for the market's tear is traders betting that the Fed will be done with rate hikes after this month, when the central bank is expected to hike them one last time.

Despite a still below-average number of IPOs, the stock market rally has helped boost returns for investors in the companies that have gone public more than twofold over last year.

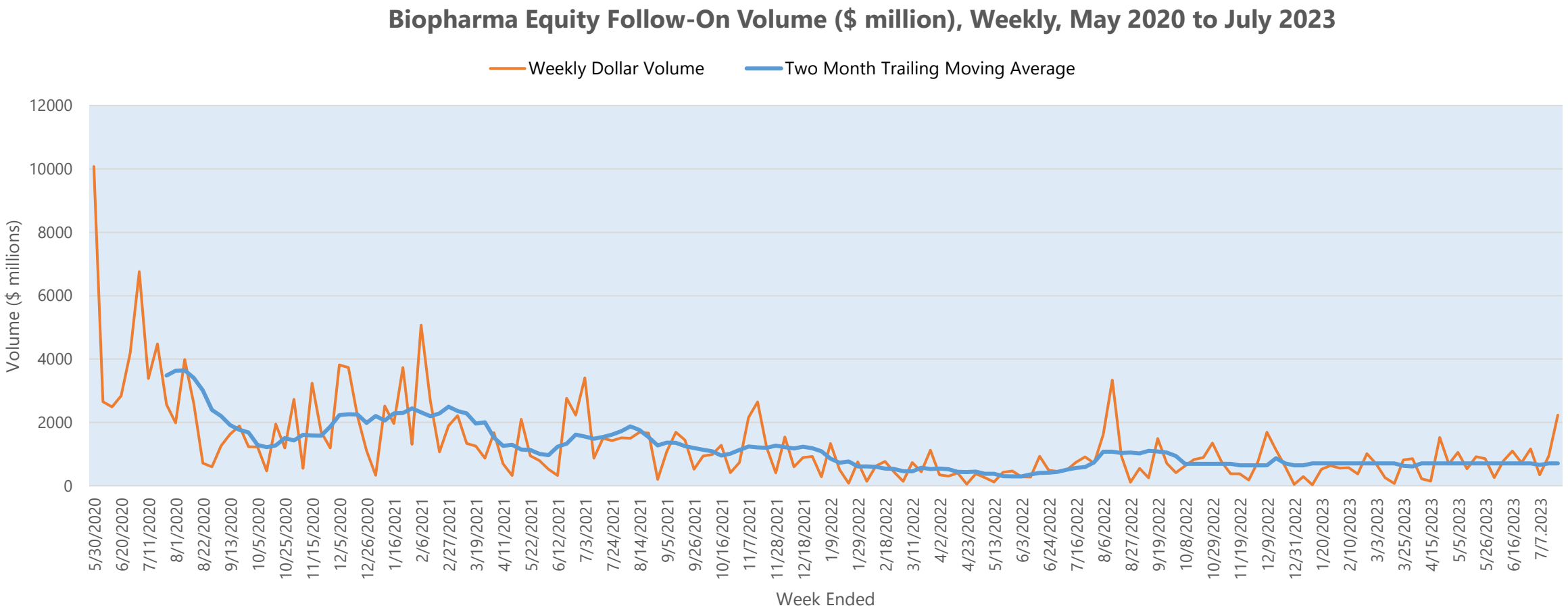
"That's been a great backdrop," Kennedy said. "Companies are able to go public at higher valuations and investors are making money."

Shares in several companies that have gone public in recent weeks have posted large returns relative to their initial offering price. Shares in restaurant chain Cava Group have more than doubled from the IPO price of $22 per share since its market debut June 15.

Source: https://apnews.com/article/ipos-stock-market-initial-public-offering-stocks-3978054d1bc8a809fd3a46094a8b799d

Last Week Was Most Active of the Year for Follow-On Offerings

Last week was the first $2bn volume week of 2023 and is consistent with a strongly recovering financing market. It was the third biggest week for follow-on's since the middle of 2021.



Source: Data from CapitalIQ and Stifel research.

Follow-on Equity Issuance Active Last Week

The eleven NASDAQ biopharma follow-on offerings so far in July have traded well with an average current/offer performance of 17.3%. Discounts have come in substantially from levels in the first half with an average of 3.6%.

Pricing Date	Target/Issuer	Amount Raised ($mm)	Deal Format	Issue Price	Market Cap at Issue Date ($mm)	Current / Offer	Discount to Previous (%)
7/20/2023	Gossamer Bio*	$212	PIPE	$1.63	$155	-17.2%	-31.5%
7/19/2023	Harrow Health	$60	Registered Offer	$17.75	$595	22.6%	17.6%
7/18/2023	argenx SE	$1,064	Registered Offer	$490.00	$28,547	11.6%	0.3%
7/18/2023	Acumen Pharmaceuticals	$130	Registered Offer	$7.75	$448	-4.5%	3.1%
7/17/2023	Janux Therapeutics	$59	Registered Offer	$12.46	$573	2.6%	-2.8%
7/16/2023	Mirum Pharmaceuticals	$210	PIPE	$26.25	$1,005	-1.4%	0.0%
7/13/2023	Caribou Biosciences	$125	Registered Offer	$6.50	$554	1.8%	20.1%
7/13/2023	Bicycle Therapeutics	$200	Registered Offer	$21.25	$868	19.5%	19.0%
7/13/2023	Savara	$80	Registered Offer	$3.00	$405	14.3%	7.3%
7/11/2023	Recursion Pharmaceuticals	$50	PIPE	$6.49	$1,298	138.4%	4.3%
7/13/2023	Iovance Biotherapeutics	$150	Registered Offer	$7.50	$1,856	2.3%	2.3%
	July 2023 Statistics		Average (N=13)		$3,300mm	17.3%	3.6%
			Median (N=13)		$595mm	2.6%	3.1%
	H1 2023 Statistics		Average (N=68)		$1,213mm	24.8%	6.9%
			Median (N=68)		$618mm	5.9%	7.3%

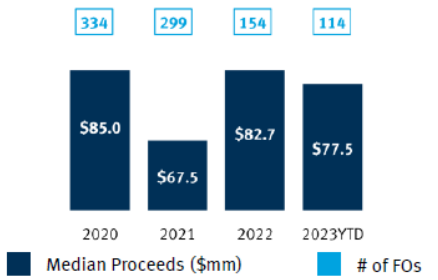
* Included 100% warrant coverage.

Source: Data from CapitalIQ and Stifel research. Follow-on offerings of companies with U.S. listings that raised $50mm or more were included.

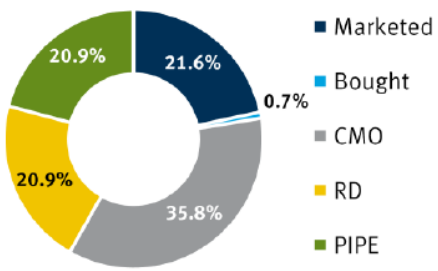
Current/Offer of Follow-On's Higher for Larger Caps

Follow-Ons Have Transitioned To A Catalyst Driven Market[1]

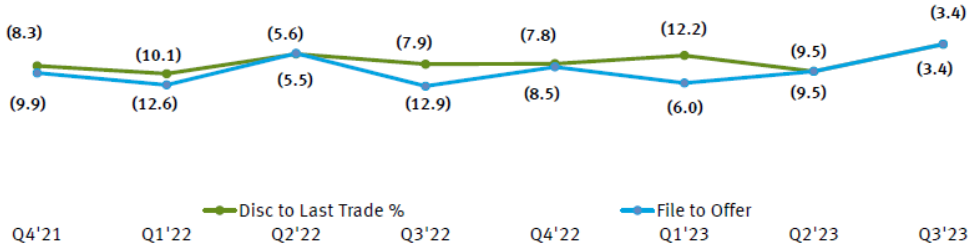
Historical biotech FOs



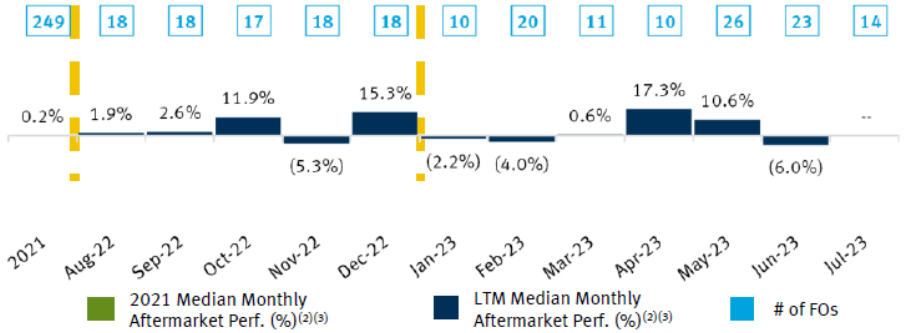
2022-2023YTD execution format



Discounts Have Remained in Line Despite Recent Volatility[2]



Aftermarket Performance Has Been Mixed[1]



Source: FactSet and Dealogic as of July 21, 2023.
Note: File to offer represents "all-in" discount for offerings with warrants.

Recent Biotech FOs By Market Cap[2]

Pricing Date	Issuer	Execution Format	Market Cap ($mm)	Total Proceeds ($mm)	File to Offer (%)	% Change: Offer to 1 Day (%)	% Change: Offer to Current (%)	Deal Catalyst	Warrants?
Recent FOs with Market Cap >$2.5bn									
07/18/23	argenx SE	Marketed	$26,972.1	$1,100.0	1.1%	7.9%	11.9%	✓	
06/28/23	Axsome Therapeutics, Inc.	CMO	3,632.7	225.0	(10.0%)	(0.0%)	0.2%		
05/08/23	Legend Biotech Corporation	RD	11,330.6	350.0	(4.5%)	7.4%	16.7%		
05/04/23	ImmunoGen Inc	Marketed	2,771.6	325.0	2.0%	5.4%	51.9%	✓	
04/19/23	Vaxcyte Inc	Marketed	3,408.9	500.2	(3.2%)	11.7%	18.4%	✓	
03/21/23	Karuna Therapeutics Inc	Marketed	6,300.4	400.0	(11.6%)	5.0%	27.1%	✓	
02/22/23	Apellis Pharmaceuticals Inc	Marketed	6,480.2	350.0	7.7%	6.3%	(45.4%)	✓	
02/02/23	Roivant Sciences Ltd	Marketed	6,015.5	200.0	(12.2%)	4.0%	47.9%	✓	
12/14/22	Prothena Corp plc	Marketed	3,027.8	183.6	(10.6%)	3.6%	15.1%	✓	
12/08/22	Prometheus Biosciences Inc	Marketed	4,009.1	500.0	14.8%	0.2%	81.7%	✓	
	Average (n=10)		**$7,394.9**	**$413.4**	**(2.6%)**	**5.1%**	**22.5%**		
	Median (n=10)		**$5,012.3**	**$350.0**	**(3.8%)**	**5.2%**	**17.5%**		
Recent FOs with Market Cap $500mm - $2.5bn									
07/20/23	ImmunityBio, Inc.	RD	$1,260.0	40.0	(24.9%)	2.3%	2.3%	✓	✓
07/19/23	Harrow Health, Inc.	CMO	550.3	60.0	(2.8%)	21.3%	22.6%	✓	
07/17/23	Janux Therapeutics, Inc.	RD	521.2	59.0	--	(2.7%)	2.6%	✓	
07/13/23	Caribou Biosciences, Inc.	CMO	537.4	125.0	(20.1%)	(3.1%)	1.8%	✓	
07/12/23	Bicycle Therapeutics plc	CMO	672.1	200.0	(3.4%)	23.5%	19.5%		
07/10/23	Iovance Biotherapeutics, Inc.	CMO	1,998.7	150.0	(14.7%)	5.7%	2.3%	✓	
06/28/23	MoonLake Immunotherapeutics	Marketed	2,421.6	400.0	8.8%	1.7%	13.3%	✓	
06/15/23	Zentalis Pharmaceuticals, Inc.	RD	1,464.9	250.0	(8.0%)	22.5%	15.6%	✓	
06/14/23	Editas Medicine, Inc.	CMO	765.5	125.0	(9.8%)	(7.2%)	(10.6%)	✓	
06/13/23	Disc Medicine Inc	Marketed	1,027.2	137.2	0.3%	--	(6.5%)	✓	
	Average (n=10)		**$1,121.9**	**$154.6**	**(7.5%)**	**6.4%**	**6.3%**		
	Median (n=10)		**$896.4**	**$131.1**	**(5.7%)**	**2.0%**	**2.5%**		
Recent FOs with Market Cap $100mm - $500mm									
07/18/23	Acumen Pharmaceuticals Inc	Marketed	$398.8	$130.0	(20.3%)	(4.4%)	(4.5%)	✓	
07/13/23	Savara Inc.	RD	453.8	80.0	1.0%	7.8%	14.3%		
06/29/23	Black Diamond Therapeutics Inc	Marketed	209.2	75.0	(12.7%)	1.0%	(10.0%)	✓	
06/28/23	CorMedix Inc.	CMO	257.4	40.0	(21.1%)	(1.5%)	(2.5%)	✓	
06/22/23	IGM Biosciences, Inc.	CMO	394.3	107.3	(9.7%)	19.1%	27.3%	✓	
06/21/23	Allovir, Inc.	CMO	461.4	75.0	(23.9%)	(15.5%)	(5.1%)	✓	
06/16/23	Verastem Oncology	CMO	181.1	85.0	(9.9%)	5.4%	1.5%		
05/31/23	Oculis Holding AG	Marketed	392.8	40.3	(4.2%)	(4.3%)	8.5%	✓	
05/22/23	Icosavax, Inc.	RD	326.0	67.8	2.9%	21.2%	14.0%	✓	
05/18/23	Prelude Therapeutics	CMO	301.9	100.0	(8.7%)	(3.0%)	(20.5%)		
	Average (n=10)		**$337.7**	**$80.0**	**(10.7%)**	**2.6%**	**2.3%**		
	Median (n=10)		**$359.4**	**$77.5**	**(9.8%)**	**(0.3%)**	**(0.5%)**		
	Average (n=30)		**$2,951.5**	**$216.0**	**(6.9%)**	**4.7%**	**10.4%**		
	Median (n=30)		**$896.4**	**$133.6**	**(8.4%)**	**3.8%**	**10.2%**		

argenx Raises $1.1 Billion in Gross Proceeds in a Global Offering

Press Release, July 18, 2023

The global offering is comprised of an offering of ordinary shares represented by ADSs in the United States and certain other countries outside of the European Economic Area and a simultaneous private placement of ordinary shares in the European Economic Area and the United Kingdom. The Company anticipates total gross proceeds of approximately $1.1 billion (approximately €979.6 million) from the sale of 1,580,981 ADSs at a price of $490.00 per ADS and the sale of 663,918 ordinary shares at a price of €436.37 per ordinary share. Each of the ADSs represents the right to receive one ordinary share, nominal value of €0.10 per share. The U.S. offering and the European private placement are currently expected to close simultaneously on July 24, 2023, subject to customary closing conditions.

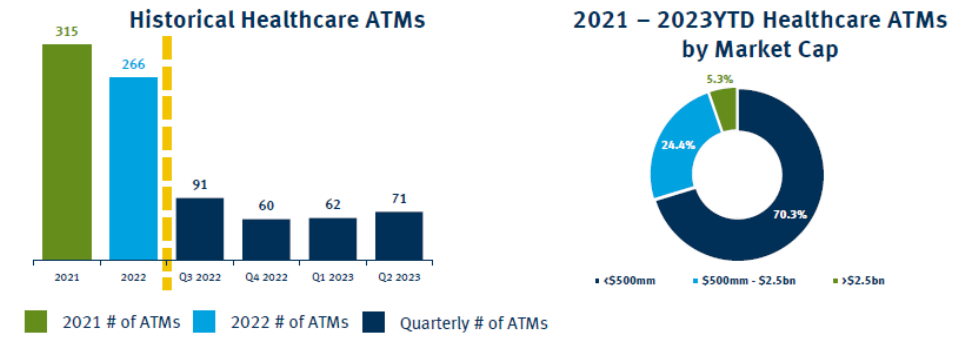
In addition, argenx has granted the underwriters of the offering a 30-day option to purchase up to 336,734 ordinary shares (which may be represented by ADSs) on the same terms and conditions.

argenx's ADSs are currently listed on the Nasdaq Global Select Market under the symbol "ARGX" and argenx's ordinary shares are currently listed on Euronext Brussels under the symbol "ARGX".

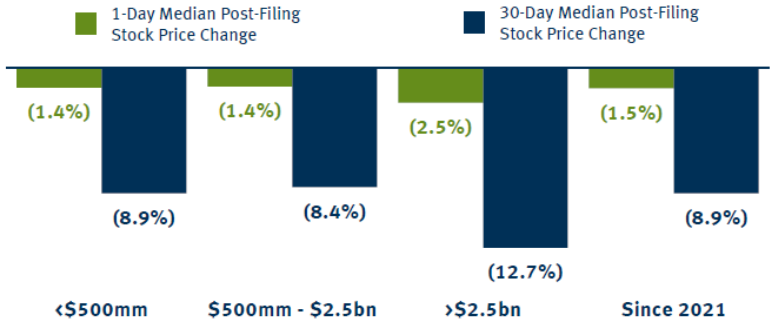
Source: https://www.argenx.com/news/argenx-raises-11-billion-gross-proceeds-global-offering

Equity Financing Alternatives Update

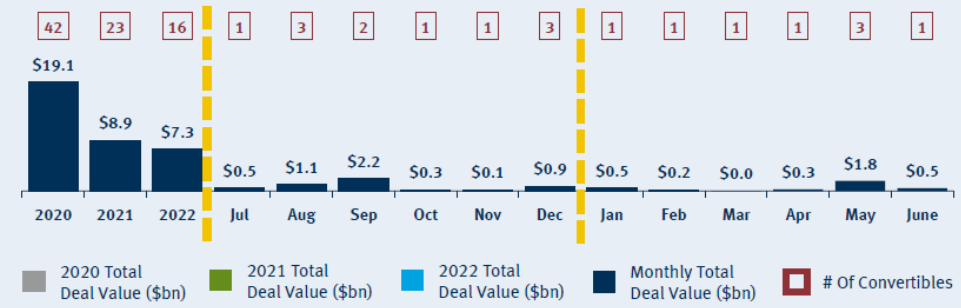
Healthcare ATMs Have Become Commonplace



Healthcare ATM Aftermarket Performance By Market Cap



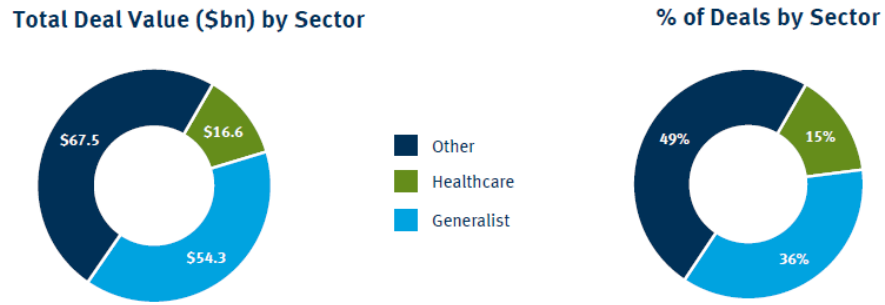
2020 – 2023YTD Healthcare Convertible Issuance



5 Most Recent Healthcare Convertible Offerings

Pricing Date	Issuer	Market Cap ($mm)	Final Deal Size ($mm)	Coupon Range	Premium Range
6/7/23	Ionis Pharmaceuticals Inc	$5,802.4	$500.0	1.500% - 2.000%	27.5% - 32.5%
5/8/23	TransMedics Group Inc	$2,309.1	$460.0	1.750% - 2.250%	27.5% - 32.5%
5/4/23	Zynex Inc	$343.5	$60.0	5.00%	15.0%
5/2/23	DexCom Inc	$45,787.5	$1,250.0	0.250% - 0.500%	37.5% - 42.5%
4/12/23	Mirum Pharmaceuticals	$892.2	$316.3	4.00%	32.5%
Mean (n=5)		$11,026.9	$517.3	2.50% 2.75%	28.0% 31.0%
Median (n=5)		$2,309.1	$460.0	1.75% 2.25%	27.5% 32.5%

SPAC Issuance By Sector Since 2021



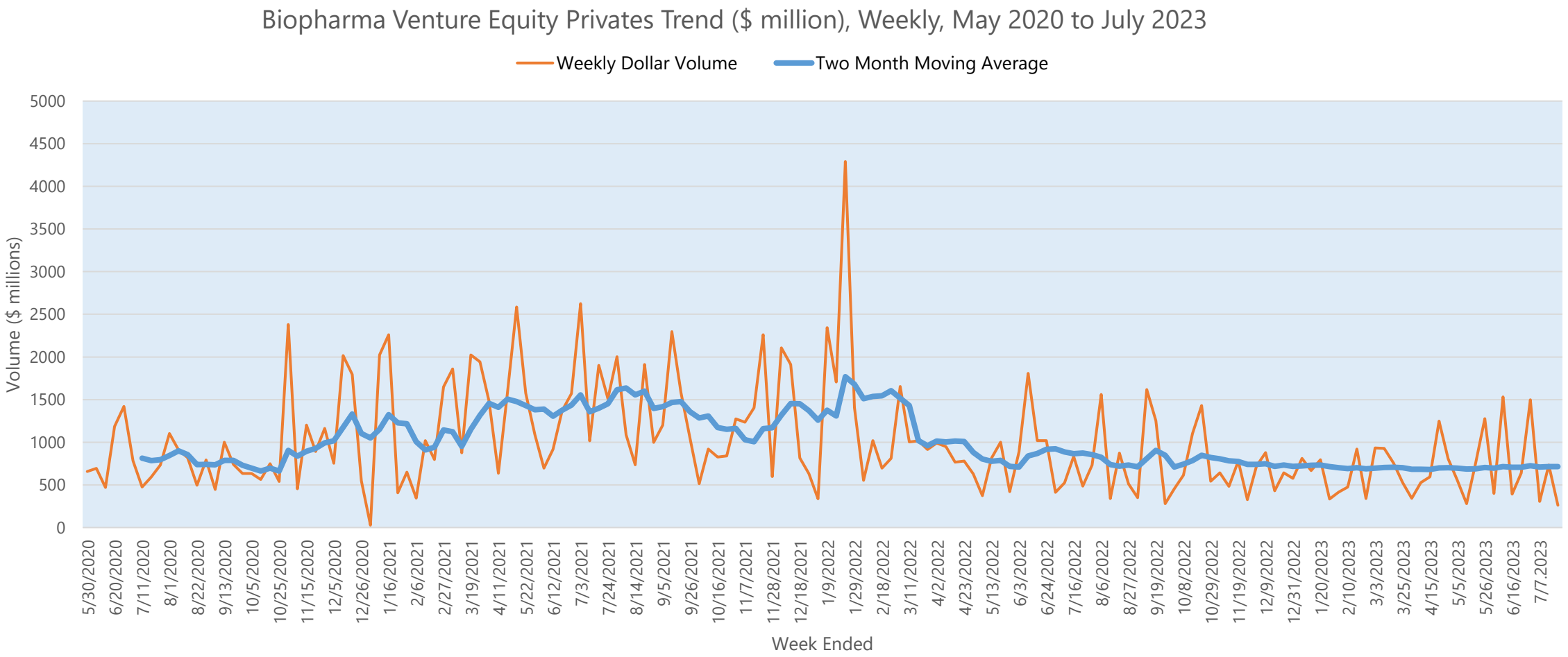
Recently Announced And Priced Healthcare SPACs

Filing Date	Pricing Date	Company	IPO Filing Size ($mm)	Base Deal Size ($mm)	Life (months)
08/26/22	-	Translational Development Acq	$150.0	-	18
08/08/22	-	BCGF Acq	87.0	-	18
04/15/22	-	Biotech Group	75.0	-	18
10/20/21	-	Artemis Acquisition	200.0	-	24
02/17/23	03/23/23	Oak Woods Acquisition Corp	$50.0	$50.0	18
04/29/22	02/09/23	Bellevue Life Sciences Acquisition Corp	60.0	60.0	9
07/01/21	02/14/22	Genesis Unicorn Capital Corp	100.0	75.0	18
12/09/21	01/06/22	Viscogliosi Brothers Acquisition Corp	75.0	75.0	18
10/21/21	12/21/21	Gardiner Healthcare Acquisitions Corp	75.0	75.0	18
05/13/21	12/20/21	Larkspur Health Acquisition Corp	75.0	75.0	18

Source: Dealogic, FactSet, PrivateRaise and SPACResearch as of July 21, 2023.

Venture Equity Market is Continuing to Slow Down

Last week saw 19 companies raise $261 million in the venture equity market. This week was quiet and, as visible with the two month moving average line shown below, volumes are continuing to drift down.



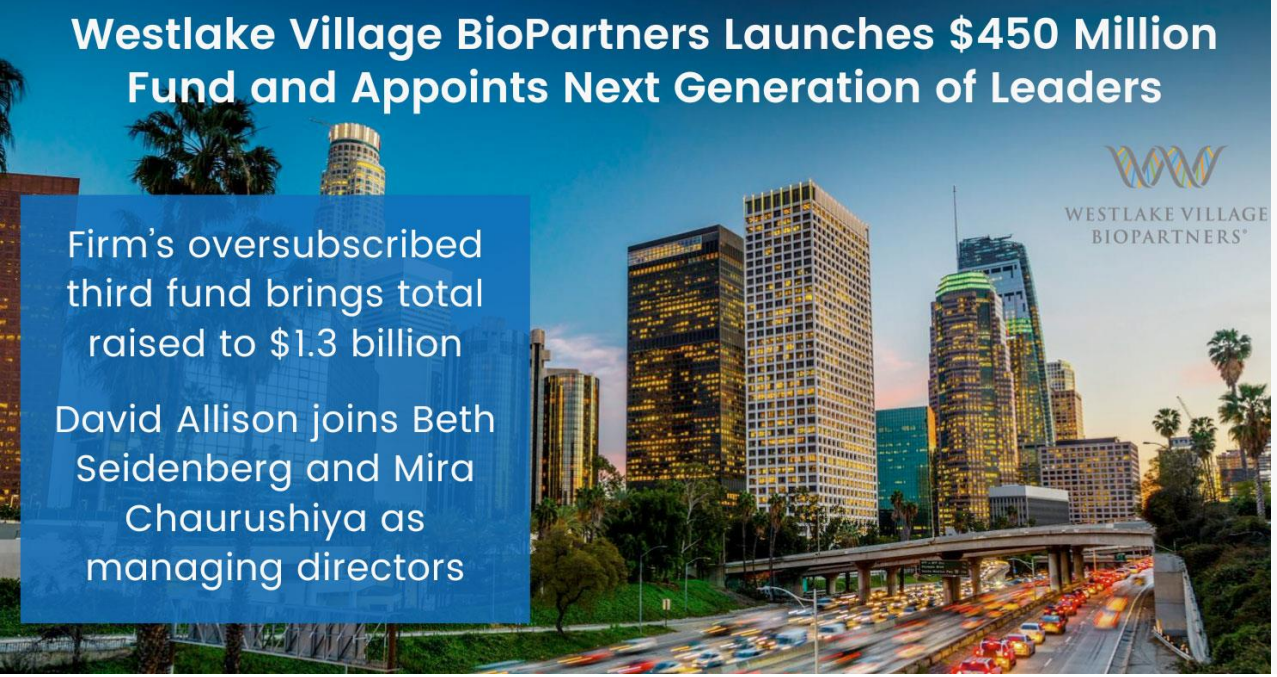
Source: Data from CapitalIQ, Crunchbase.

Biopharma Venture Equity Financings This Month

Only one announcement in the first three weeks of July involving a raise over $100mm. RA Capital the most active investor.

Company	Announcement Date	Amount Raised ($mm)	Round	Lead Investor	Stage at Funding	Primary TA	Company Focus	Modality / Technology	Pre-Money Valuation ($mm)	HQ Country
septerna	07/11/2023	$150	Series B	RA Capital	Platform / Discovery	Neurologic	Undruggable GPCRs	Small Molecule	$100	United States
SPYGLASS	07/10/2023	$90	Series C	RA Capital	Phase I	Ophthalmic	Lasting intraocular drug delivery / glaucoma	Small Molecule	$33.5	United States
Crossbow therapeutics	07/11/2023	$80	Series A	MPM Capital	Platform / Discovery	Cancer	TCR mimetic antibodies for MHC peptides in cancer	Antibody	NA	United States
Arthrosi THERAPEUTICS, INC.	07/11/2023	$75	Series D	Undisclosed	Phase II	Inflammation	New drug for gout	Small Molecule	NA	United States
tenpoint THERAPEUTICS	07/12/2023	$70	Series A	F-Prime Capital Partners	Platform / Discovery	Ophthalmic	In vivo reprogramming of ophthalmic cells to reverse vision loss.	Cell Therapy	NA	United Kingdom
renibus therapeutics	07/18/2023	$63	Series B	Family Offices	Phase II	Renal	Inducer of Nrf2, IL-10, and ferritin for post cardiac surgery recovery	Other Tech	NA	United States
SURGE	07/19/2023	$32	Series B	Bioluminescence	Phase I	Cancer	Intraoperative drug candidate for bladder cancer surgery	Immunotherapy	$26	United States

Source: Data from DealForma, Stifel research.



LOS ANGELES, Calif., July 17, 2023 – Westlake today announced the launch of its third fund of $450 million to incubate and grow early stage next-generation biotechnology companies in the Los Angeles region and beyond. The new fund will be managed by founding managing director Beth Seidenberg, M.D., managing director Mira Chaurushiya, Ph.D., and David Allison, Ph.D., who was recently appointed managing director.

"This new fund will enable us to continue to do what we do best – build great companies from the ground up that make a difference for patients and generate outsized returns for investors regardless of market conditions," said Dr. Seidenberg. "Our investors recognize our strategy is working and have demonstrated their commitment through this new investment."

Source: https://westlakebio.com/westlake-village-biopartners-launches-450-million-fund-and-appoints-next-generation-of-leaders/

An Innovation Supply Chain: Pfizer Taps Flagship for 10-Program Pipeline Pact Worth $7B in Biobucks

Gabrielle Masson, *Fierce Biotech*, Jul 18, 2023

Pfizer and Flagship Pioneering have each put down $50 million to build a new pipeline of 10 programs, with the Big Pharma offering the VC firm and its bioplatform companies the chance to make up to $700 million in biobucks for each successful drug.

“The scale, the scope and the intent is really very distinctive,” Paul Biondi, president of Flagship’s Pioneering Medicines initiative and executive partner at Flagship, said about the deal.

Pfizer's CEO Albert Bourla, Ph.D., and chief scientific officer Mikael Dolsten, M.D., Ph.D., have “clearly demonstrated a sense of urgency in creating and delivering important novel medicines to patients,” and that proactivity extends to this partnership, Biondi told Fierce Biotech in an interview.

The collective $100 million upfront will go toward leveraging Flagship’s ecosystem of therapeutic platforms to explore opportunities that could lead to the development of 10 single-asset programs. While Moderna is included in the Flagship ecosystem, Biondi said the partnership will more likely include companies in earlier-stage development.

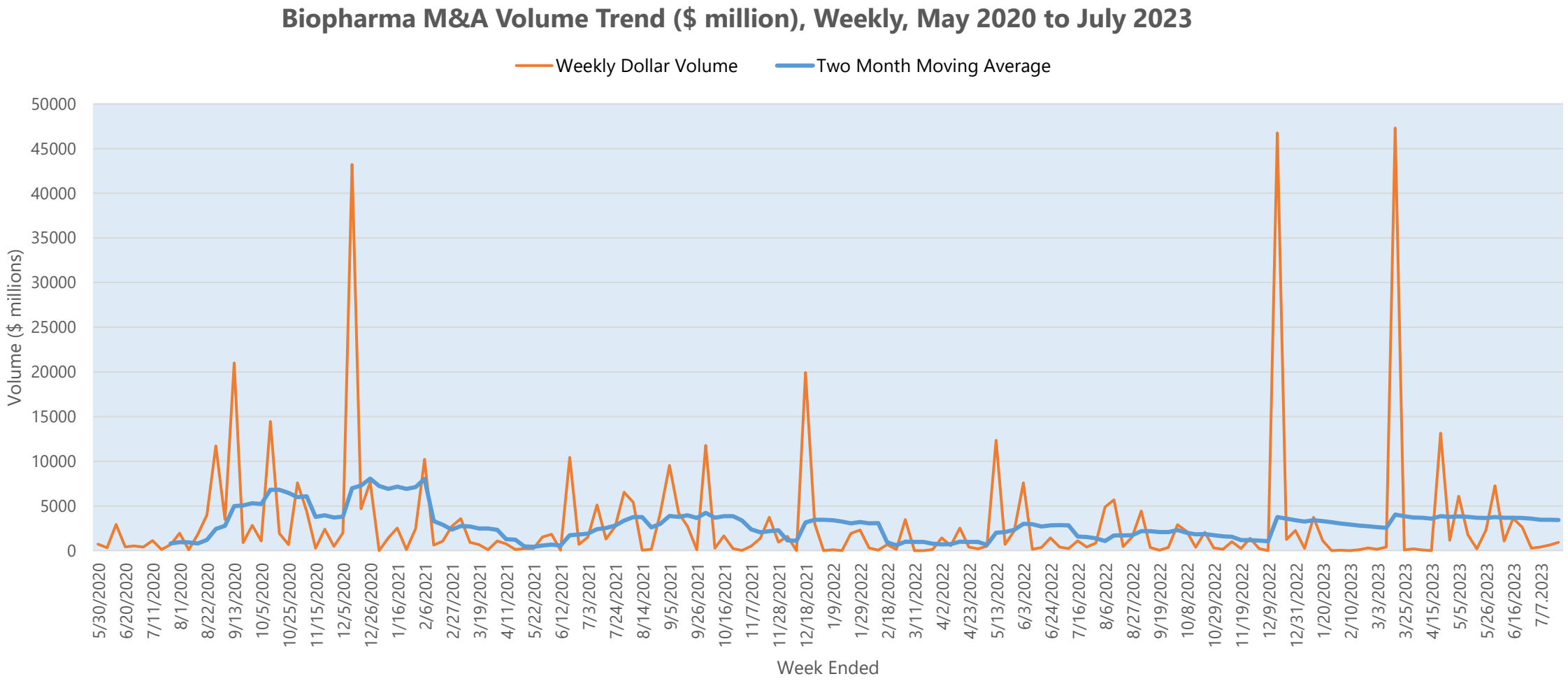
Source: https://www.fiercebiotech.com/biotech/pfizer-flagship-launch-10-program-pipeline-pact-could-be-worth-7b-biobucks

M&A Update

Group meeting in laboratory. Source: Getty Images.

Last Week Saw $910 Million in M&A Volume

Last week saw moderate biopharma M&A volume. The largest deals were Novartis' acquisition of DTX Pharma and Sosei's acquisition of the Asian assets of Idorsia.



Source: S&P, CapitalIQ

Novartis to Acquire DTx Pharma

SAN DIEGO, July 17, 2023 /PRNewswire/ -- DTx Pharma, a preclinical stage biotechnology company addressing the delivery challenges of oligonucleotide therapeutics with its Fatty Acid Ligand Conjugated OligoNucleotide (FALCON™) platform, announced today that it has been acquired by Novartis. The FALCON platform enables the delivery and activity of small interfering RNA (siRNA) therapeutics to tissues beyond the liver, enhancing biodistribution and cellular uptake. DTx Pharma's lead program is currently in preclinical development, with FDA Orphan Drug Designation, for the treatment of Charcot-Marie-Tooth Disease Type 1A (CMT1A). CMT1A is a progressive, neuromuscular, autosomal-dominant disease that can lead to life-long loss of muscle function and disability.

Currently, there are no approved therapeutics addressing PMP22, the underlying genetic cause of CMT1A, for the estimated 150,000 patients living with the debilitating disease in the United States and Europe. DTx Pharma's lead asset, DTx-1252, is a novel, potential first-in-class, FALCON siRNA candidate targeting PMP22. The asset boasts a robust preclinical package, demonstrating the reversal of disease in preclinical rodent models and translation to higher species with IND-enabling studies progressing well.
"I am thrilled that Novartis will be moving forward with our CMT1A therapeutic program and the FALCON platform. With its resources and capabilities in neuromuscular diseases, Novartis is well positioned to accelerate the development of DTx-1252 and provide hope to patients, who are desperately in need of therapy," said Artie Suckow, Ph.D., co-founder and CEO of DTx Pharma. "I am also extremely proud of the commitment and passion of our team, which has established DTx Pharma as a leader in extra-hepatic delivery of siRNA, as demonstrated by our work to advance the first investigational FALCON siRNA designed to be delivered to the peripheral nervous system to treat the genetic cause of CMT1A."

In addition to the CMT1A program, Novartis has acquired full rights to the FALCON platform and two other early-stage programs in neuromuscular and central nervous system (CNS) indications.

Under the terms of the agreement, Novartis will make an upfront payment of $500M and additional payments of up to $500M upon completion of pre-specified milestones.

Source: https://investor.lilly.com/news-releases/news-release-details/lilly-acquire-dice-therapeutics-advance-innovation-immunology

Idorsia Sells its Asia Pacific Operations to Sosei Heptares for CHF 400 Million

Alschwil, Switzerland, July 20, 2023 Idorsia Ltd (SIX: IDIA) today announced the sale of its operating businesses in the Asia Pacific (ex-China) region ("Territory"), including assignment of PIVLAZ (clazosentan) and license rights to daridorexant in those territories, to Sosei Group Corporation (TSE: 4565; 'Sosei Heptares') for a total consideration of CHF 400 million.

Jean-Paul Clozel, Chief Executive Officer of Idorsia, commented:
"Dr Satoshi Tanaka and his team in Idorsia Japan have consistently demonstrated their ability to deliver high-quality clinical development studies, most recently reporting positive Phase 3 results with daridorexant. They also developed, registered, and successfully brought PIVLAZ to a specialty market, serving over 5'000 patients with a rare form of stroke in the first year alone. The excellence displayed by the organization has been recognized by Sosei, hence a deal that creates value for both companies. I'm particularly happy that we are maintaining our relationships to the team and our ability to reach patients in the territory with our pipeline products."

Chris Cargill, President, and Chief Executive Officer of Sosei Heptares, commented:
"We have patiently and diligently been searching for the right opportunity to accelerate our mission to deliver life-changing new medicines to patients. This transaction with Idorsia is truly transformational and achieves one of our key strategic objectives, establishing Sosei Heptares as a fully integrated Japan-focused pharmaceutical business, with growing commercial sales and an expected new product launch next year. The addition of a highly experienced clinical development and entrepreneurial commercial team in Japan led by Dr Satoshi Tanaka, one of the country's most successful drug developers in recent times, fast-tracks our vision to become one of Japan's global biopharmaceutical champions."

About the transaction
The transaction includes the acquisition by Sosei Heptares of Idorsia's affiliates in Japan and South Korea, the assignment of the license for PIVLAZ (clazosentan) and all intellectual property and know-how for the territory, and a co-exclusive license for daridorexant – further to the agreement in place with Mochida Pharmaceutical. The transaction also includes an option for Sosei Heptares – upon payment of separate option fees – to license cenerimod and lucerastat for the development and commercialization in the Territory.

Idorsia will supply PIVLAZ and daridorexant to Sosei Heptares. In addition, there will be transition service agreements (TSA) between Idorsia and Sosei Heptares mainly for regulatory/filing activities, clinical development, CMC (Chemistry, Manufacturing and Controls), and IT.

Source: https://www.idorsia.com/media/news-details?newsId=3041539

Licensing Activity Brisk So Far in July 2023

Licensing volume has been robust but upfronts have been modest (at least announced upfronts). Most transactions have been discovery stage. Roughly a third of licensor's so far this month have been Chinese, echoing the growing importance of this geography.

Date Announced	Licensor	Licensee	Deal Stage	Deal Type	Primary Tech	Primary TA	Upfront Cash and Equity ($mm)	Total Deal Value ($mm)
7/5/2023	CAMP4 Therapeutics	Fulcrum Therapeutics Inc.	Platform / Discovery	Dev and Commercial License	Small Molecule	Hematologic	n/a	$70
7/5/2023	F-star Therapeutics	Takeda Pharmaceutical	Platform / Discovery	Dev and Commercial License	Antibody	Cancer	n/a	$1,000
7/5/2023	Beijing Biocytogen Co. Ltd.	Pheon Therapeutics	Platform / Discovery	Dev and Commercial License	Antibody	Cancer	n/a	n/a
7/5/2023	Sirnaomics Inc.	EDIRNA Inc.	Platform / Discovery	Dev and Commercial License	RNA	Cancer	n/a	n/a
7/5/2023	Altamira Therapeutics	Heqet Therapeutics s.r.l.	Platform / Discovery	Option to License	RNA	Cardiovascular	n/a	n/a
7/5/2023	JADBio – Gnosis DA S.A.	DiamiR LLC	Diagnostic - Any	R&D Only	AI	Neurologic	n/a	n/a
7/6/2023	MaxCyte Inc.	Lyell Immunopharma Inc.	Platform / Discovery	Dev and Commercial License	Cell Therapy	Cancer	n/a	n/a
7/10/2023	Zhejiang Doer Biologics	BioNTech SE	Preclinical / IND	Dev and Commercial License	Unknown	Unknown	NA	n/a
7/10/2023	4D Molecular Therapeutics	Astellas Pharma Inc.	Platform / Discovery	Dev and Commercial License	Vector	Ophthalmic	$20	$963
7/10/2023	Nanobiotix S.A.	Janssen	Phase II	Dev and Commercial License	Small Molecule	Cancer	$60	$2,670
7/10/2023	MaxCyte Inc.	viTToria Biotherapeutics Inc	Platform / Discovery	Dev and Commercial License	Cell Therapy	Cancer	n/a	n/a
7/10/2023	Duality Biologics	BeiGene Ltd.	Preclinical / IND	Option to License	Antibody Conjugate	Cancer	n/a	$1,300
7/10/2023	Elsie Biotechnologies Inc.	GSK	Platform / Discovery	R&D Only	RNA	Unknown	n/a	n/a
7/12/2023	Argenx N.V.	Raya Therapeutic Inc.	Preclinical / IND	R&D Only	Small Molecule	Neurologic	n/a	n/a
7/13/2023	KSQ Therapeutics Inc.	Roche	Phase I	Dev and Commercial License	Small Molecule	Cancer	n/a	n/a
7/14/2023	GeneQuantum Healthcare	InxMed Co. Ltd.	Platform / Discovery	Dev and Commercial License	Small Molecule	Cancer	n/a	n/a
7/17/2023	Scipher Medicine	Ionis Pharmaceuticals Inc.	Platform / Discovery	Dev and Commercial License	Small Molecule	Cardiovascular	n/a	n/a
7/17/2023	leadXpro AG	Cumulus Oncology	Platform / Discovery	Option to License	Small Molecule	Cancer	n/a	n/a
7/17/2023	Sangamo Therapeutics Inc.	Eli Lilly	Platform / Discovery	Option to License	Vector	Neurologic	n/a	$1,190
7/17/2023	Eleven Therapeutics Ltd.	Novo Nordisk	Platform / Discovery	R&D Only	DNA	Cardiovascular	n/a	n/a
7/18/2023	Twist Bioscience Corp.	Cancer Research Horizons	Platform / Discovery	Dev and Commercial License	Antibody	Cancer	n/a	n/a
7/18/2023	Flagship Pioneering	Pfizer Inc.	Platform / Discovery	Option to License	Unknown	Unknown	$100	$800
7/19/2023	Riparian Pharmaceuticals Inc.	Pfizer Inc.	Preclinical / IND	Option to License	Unknown	Cardiovascular	n/a	n/a
7/19/2023	Biotheus Inc.	BioNTech SE	Phase I	Option to License	Antibody	Cancer	n/a	n/a
7/20/2023	Recludix Pharma Inc.	Sanofi S.A.	Preclinical / IND	Dev and Commercial License	Small Molecule	Autoimmune	n/a	$1,325
7/20/2023	Sangamo Therapeutics Inc.	Chroma Medicine Inc.	Platform / Discovery	Option to License	Protein	Unknown	n/a	n/a
7/20/2023	RenovoRx Inc.	Imugene Ltd.	Platform / Discovery	R&D Only	Gene Therapy	Cancer	n/a	n/a

Source: DealForma

BUSINESS | HEALTH CARE | HEALTH

Big Pharma Bets Big on China

Western drugmakers have aligned themselves with Beijing's health priorities and are tapping local startups for innovative medicines

By Clarence Leong Wall Street Journal

July 23, 2023 7:00 am ET

SINGAPORE—Global pharmaceutical companies are bucking one of the biggest trends in business right now: they are still betting on China at a time when many multinationals are shifting their focus elsewhere.

Western drug companies including Pfizer and AstraZeneca have recently said they are committed to helping China solve the challenges posed by its aging population and have struck multimillion-dollar licensing deals with local companies.

Their moves signal the staying power of the Chinese market despite the risk of being caught by rising Sino-U.S. tensions and a push in Washington and European capitals to reduce reliance on China.

Driving demand in China is the rapidly rising share of the population who are living longer with chronic lifestyle diseases, and a wealthier middle class that cares more about health. Beijing has vowed to improve the quality of public healthcare and extend basic insurance that covers more than 95% of the population.

Source: https://www.wsj.com/articles/big-pharma-bets-big-on-china-2383e6ec

Disclosure

STIFEL | Healthcare

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