Biopharmaceutical Sector

Weekly Update – Feb 26, 2024

STIFEL | Healthcare

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

Recent issues in case you missed and want to read:

Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Jan 22, 2024 (AI in medicine)
Jan 15, 2024 (FDA Commissioner Priorities)
Jan 5, 2024 (Sector Outlook for 2024)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 22, 2023 (Bullish on Biotech)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
October 23, 2023 (ESMO Review)
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October 9, 2023 (Biosimilars, M&A)
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September 25, 2023 (Target ID)
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August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on Feb 23, 2024.

The next event will be on March 1, 2024.

Feb 23, 2024. Session: https://twitter.com/i/spaces/1kvKpvZaddPJE

Please join us.

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

The week of March 18 will feature over 5,000 biopharma professionals in Barcelona for Bio-Europe. We hope to meet you there.

To meet with Stifel @ Bio-Europe
yeungn@stifel.com

Biopharma Market Update

The XBI Closed at 94.75 Last Friday (Feb 23), Up 1.7% for the Week

The XBI is up 6.1% since the year began. The biotech market's momentum continued as Treasury yields flattened out for the week. Next week will see release of PPE inflation numbers which will likely influence the course of the biotech market.

Biotech Stocks Up Again Last Week

Return: Feb 17 to Feb 23, 2024

Nasdaq Biotech Index: +1.8%
Arca XBI ETF: +1.7%
Stifel Global Biotech EV (adjusted): +1.5%*
S&P 500: 1.7%

Return: Jan 1 to Feb 23, 2024

Nasdaq Biotech Index: +2.8%
Arca XBI ETF: +6.1%
Stifel Global Biotech EV (adjusted): +21.5%*
S&P 500: +6.7%

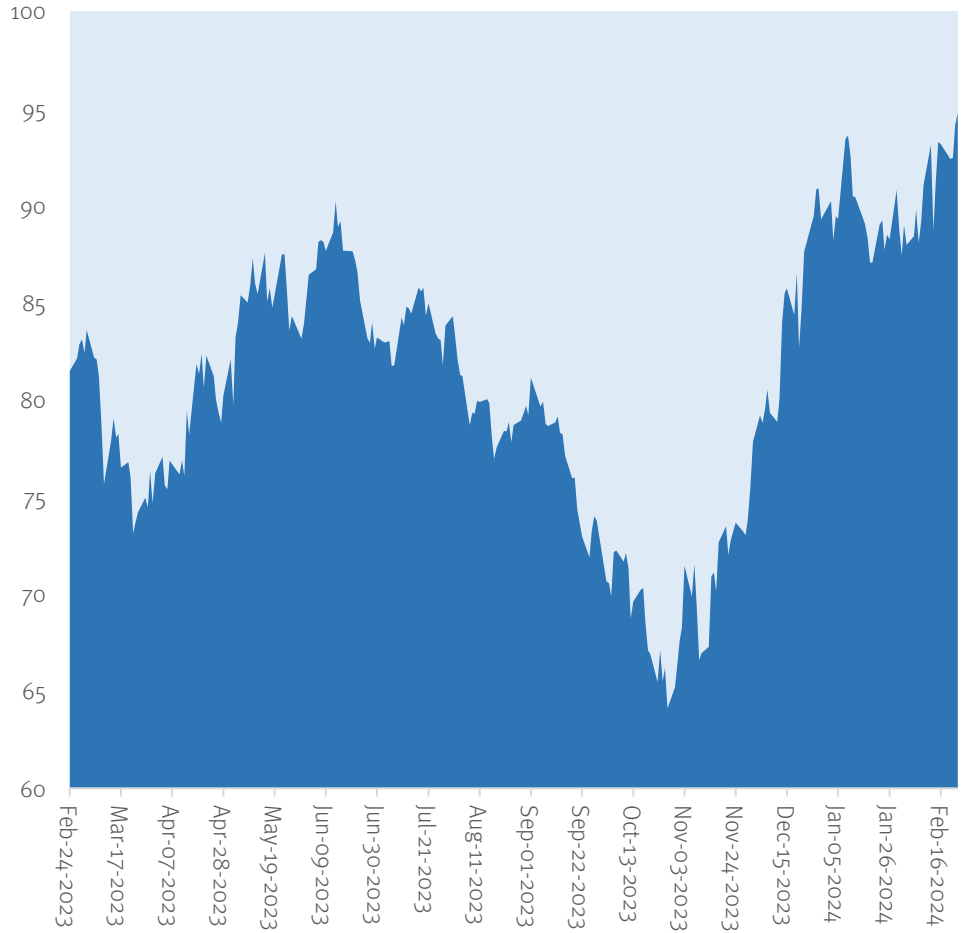
VIX Down

Jan 20, 2023: 19.9%
May 26, 2023: 18.0%
July 21, 2023: 13.6%
Sep 29, 2023: 17.3%
Oct 27, 2023: 21.2%
Dec 29, 2023: 12.45%
Jan 26, 2024: 13.26%
Feb 16, 2024: 14.2%
Feb 23, 2024: 13.5%

10-Year Treasury Yield Flat

Jan 20, 2023: 3.48%
May 26, 2023: 3.8%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Oct 27, 2023: 4.86%
Dec 29, 2023: 3.88%
Jan 26, 2024: 4.15%
Feb 16, 2024: 4.3%
Feb 23, 2024: 4.26%

XBI, Feb 24, 2023 to Feb 23, 2024



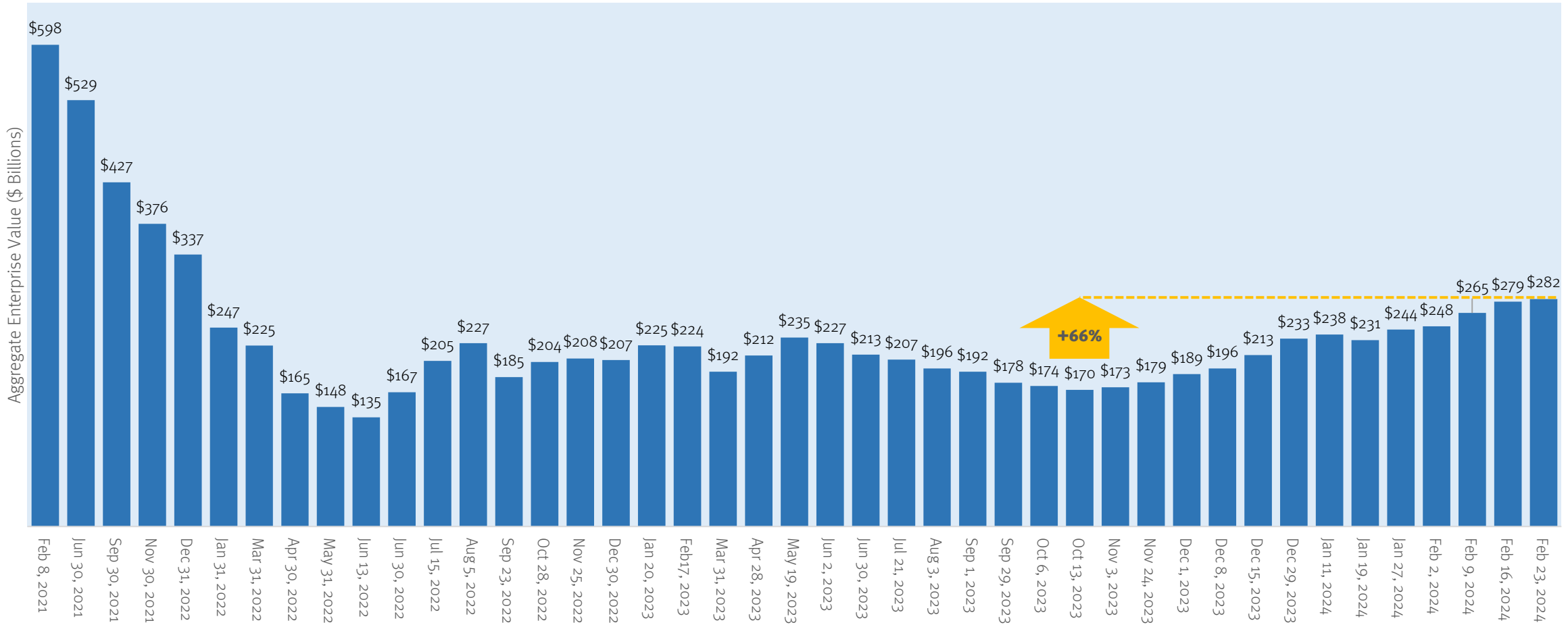
* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

Total Global Biotech Sector Value Rose 1.5% Last Week

The total enterprise value of the global biotech sector is up 21.5% for the year to date on an addition/exit corrected basis. The rally that started four months ago continued last week but not quite at the same pace as before. The biotech market has been up 14 of the last 16 weeks. The market is up 66% from its October nadir but down 47% from its Pandemic peak.

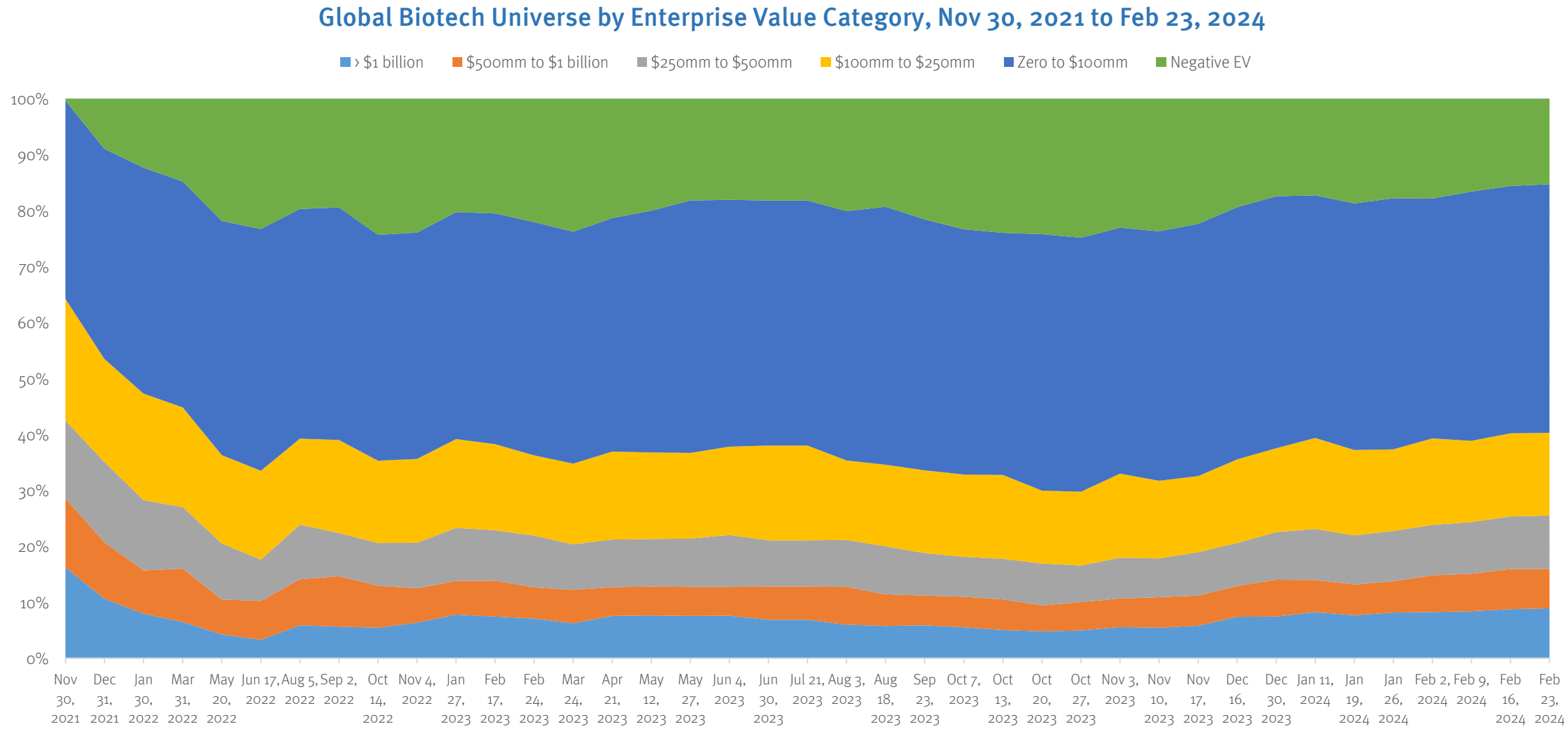
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Feb 23, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

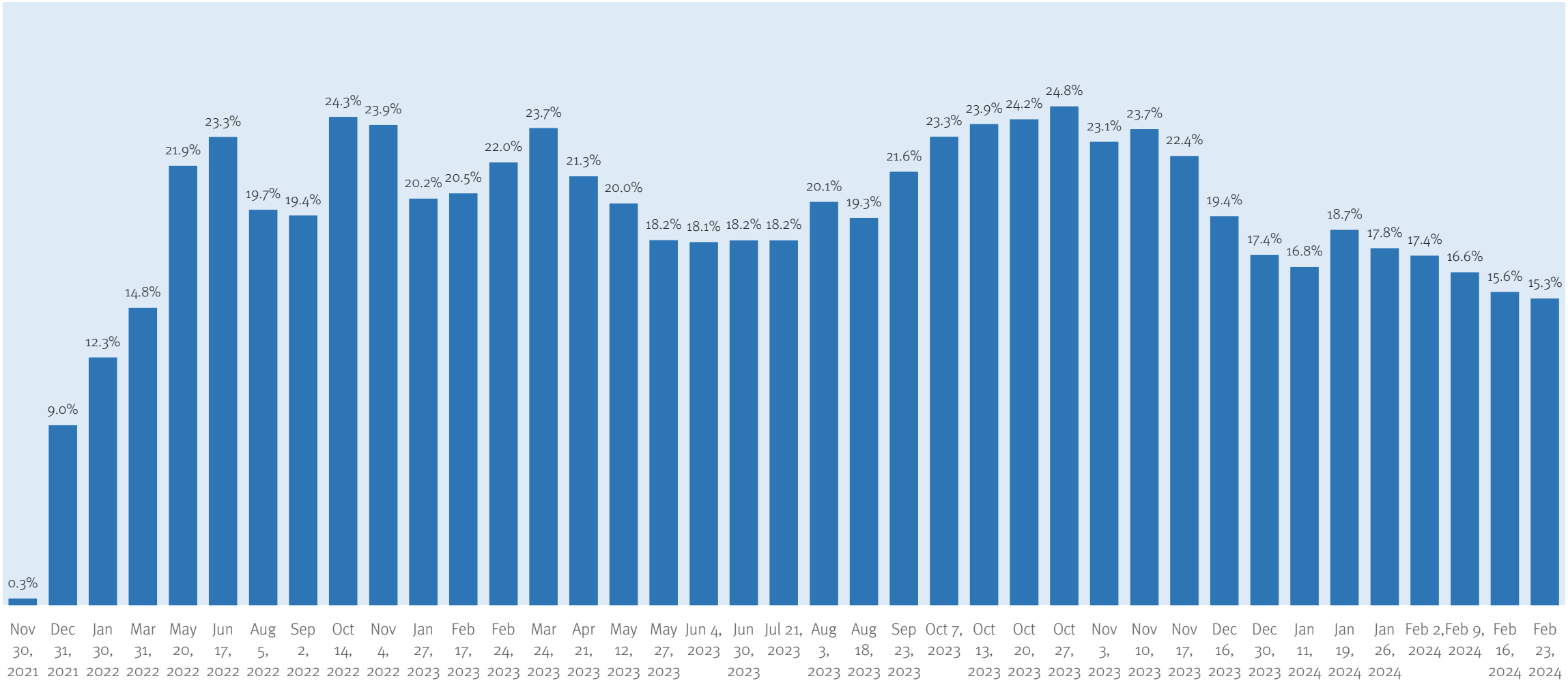
Last week saw continued growth in the fraction of the global biotech population with an EV over $100 million. The population of larger biotechs ($500mm and up EV) is also growing steadily.



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

Major Shrinkage in Negative EV Global Biotech Population

Percent of Global Biotechs with Negative Enterprise Value, Nov 2021 to Feb 2024



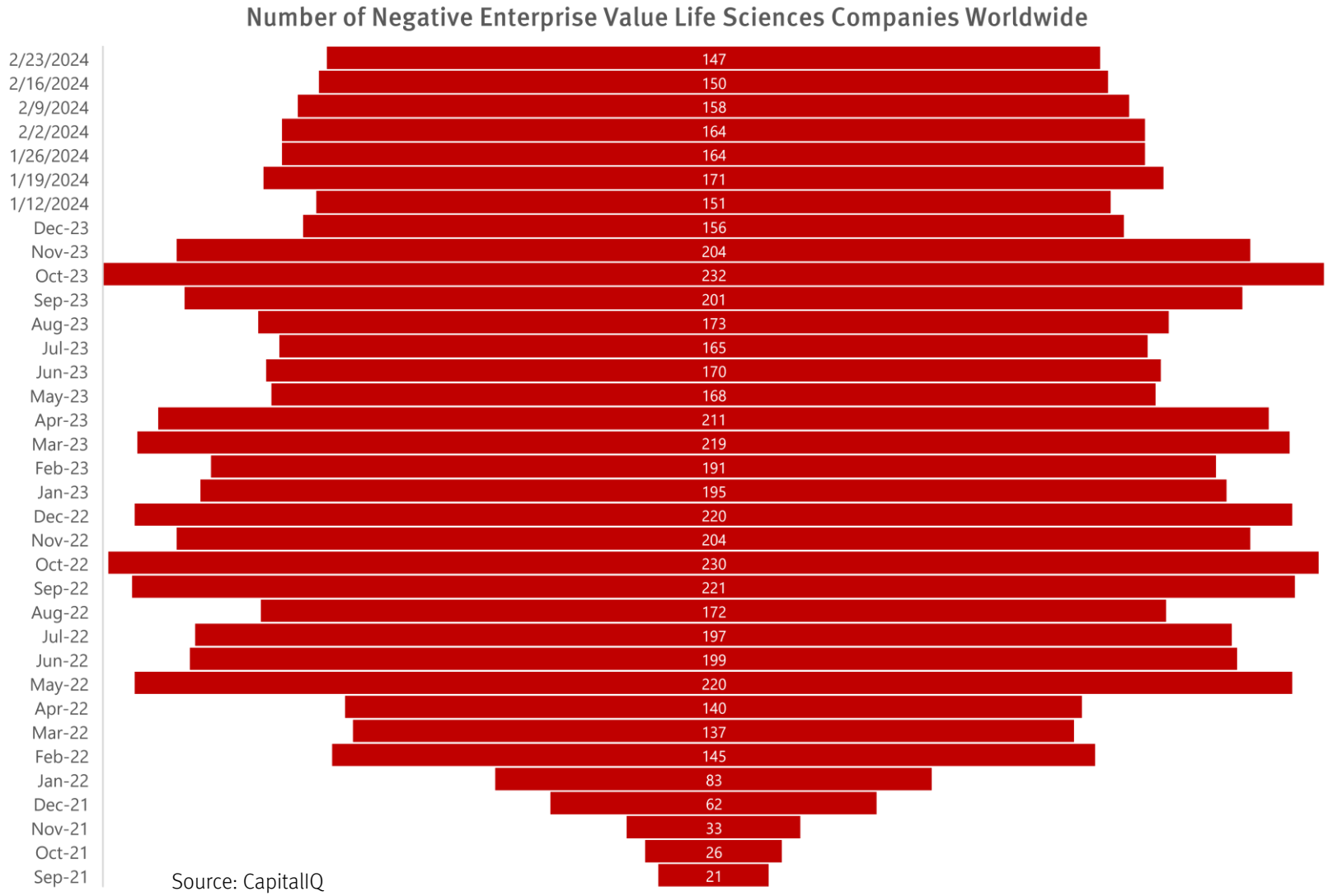
Life Sciences Sector Total Value Up Last Week by 1.8%

Last week saw the life sciences sector gain $169 billion in value. The best performing sectors were pharma services and commercial pharma while HCIT saw a significant value drop (Teladoc dropped 30% last week).

Sector	Firm Count	Enterprise Value (Feb 23, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,298	1.3%	0.1%	-1.8%
Biotech	804	$281,514	1.5%	13.2%	-5.1%
CDMO	40	$150,391	0.7%	4.1%	-20.8%
Diagnostics	81	$269,295	0.8%	1.1%	4.3%
OTC	30	$28,139	0.6%	1.3%	-4.8%
Commercial Pharma	719	$6,285,297	2.0%	5.6%	13.5%
Pharma Services	39	$198,357	2.9%	1.9%	-5.1%
Life Science Tools	51	$710,831	1.1%	5.7%	-2.6%
Medical Devices	181	$1,729,222	1.8%	4.8%	10.3%
HCIT	11	$21,125	-4.6%	-2.2%	-24.1%
Total	2037	$9,745,469	1.8%	5.4%	10.5%

Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Declined in Last Week



Source: CapitalIQ

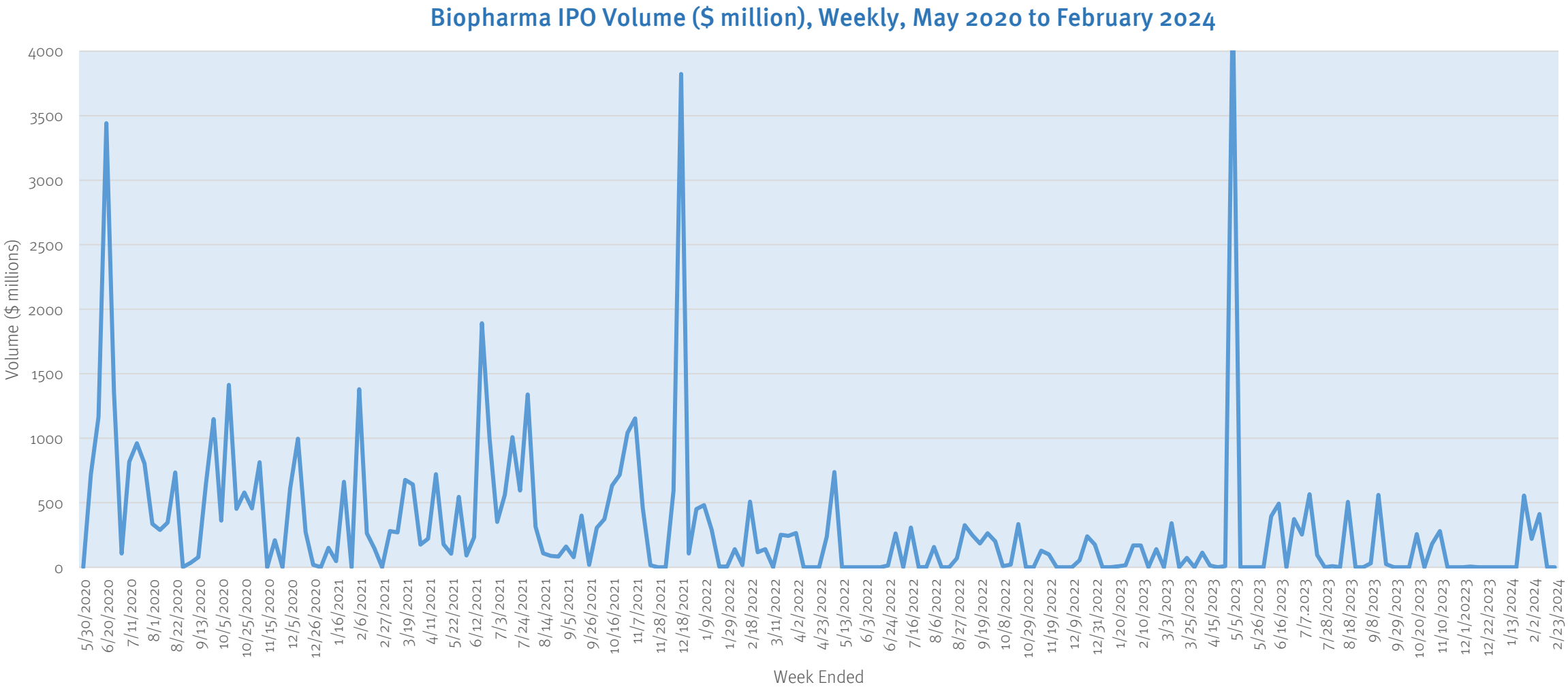
The count of negative EV life sciences companies worldwide dropped to 147 from 150 last week.

We haven't seen this few negative EV companies since April 2022.

Capital Markets Update

IPO Market Took a Breather Last Week

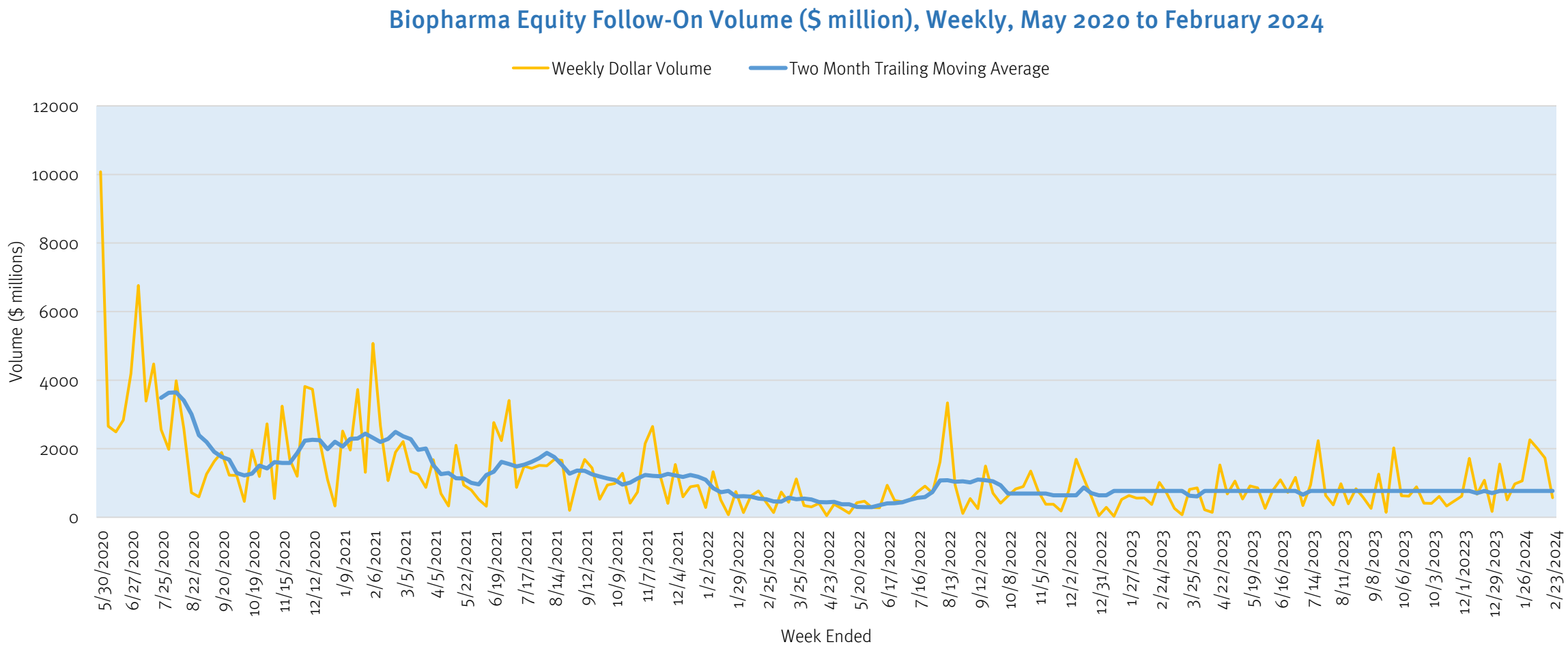
The IPO market took a break last week.



Source: Data from CapitalIQ and Stifel research.

Follow-On Market Active Last Week

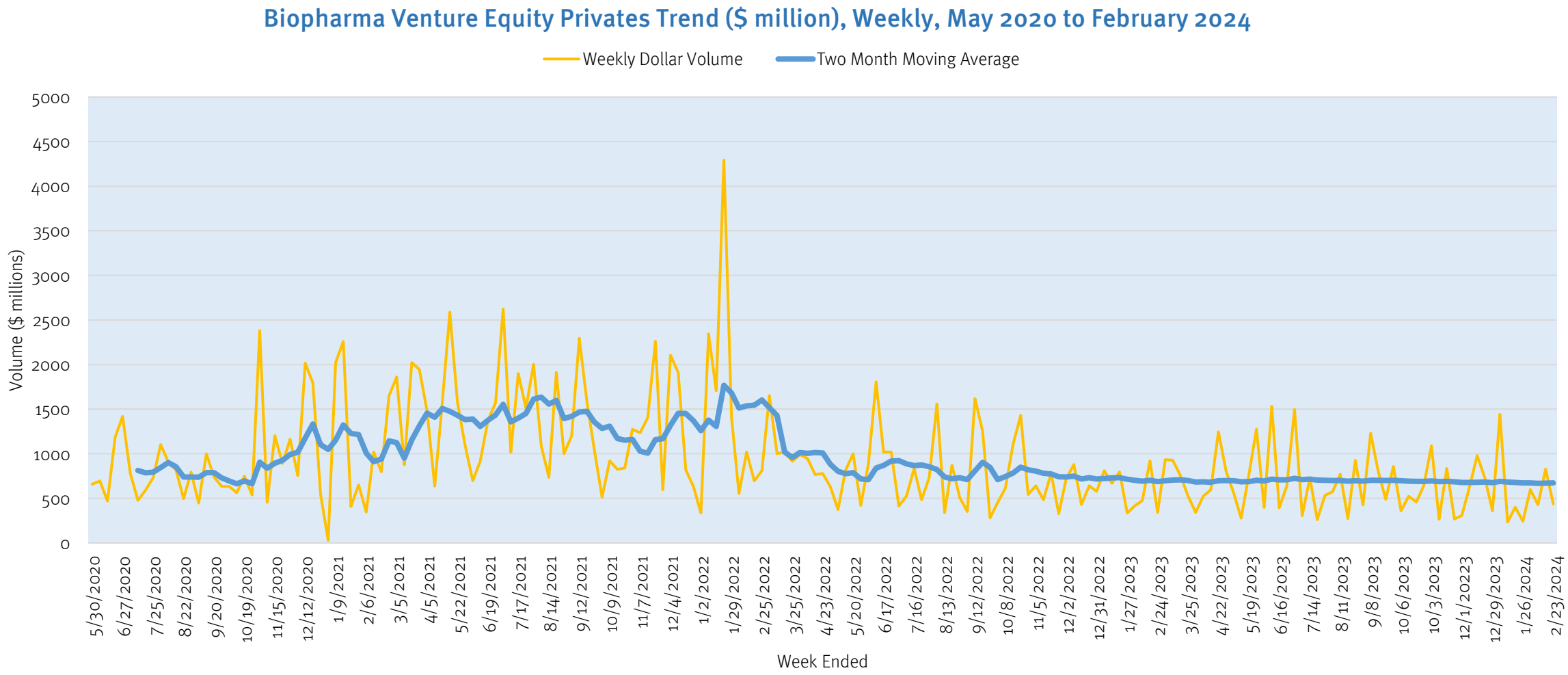
Last week saw the pace of follow-on issuance drop by over 70% from recent weeks as biotechs largely ceased to have fresh financials. 10-K's will be coming out in the next month or so and we should start to see a big pick up in activity in Mid-March to April.



Source: Data from CapitalIQ and Stifel research.

Venture Private Volume Quiet Last Week

Last week saw $437 million in privates deal volume. It was a significantly quieter week than the week before.



Source: Data from CapitalIQ, Crunchbase.

Frontier Medicines Announces Oversubscribed $80 Million Series C Financing to Support Progress of Clinical-Stage Pipeline

BOSTON and SOUTH SAN FRANCISCO, Calif., Feb. 22, 2024 (GLOBE NEWSWIRE) -- Frontier Medicines Corporation, a precision medicine company seeking to unlock the proteome to advance transformational therapies against otherwise undruggable disease-causing targets, today announced the close of an oversubscribed $80 million Series C financing. The financing was co-led by Deerfield Management Company and Droia Ventures, with significant participation from Galapagos NV (Euronext & NASDAQ: GLPG) as a strategic investor, and contributions from new and existing investors including DCVC Bio, MPM Capital, and RA Capital Management. This Series C financing brings the total capital raised since Frontier's founding to $235.5 million.

"At Galapagos, we are focused on breakthrough science and innovation to address high unmet medical needs," said Dr. Paul Stoffels, CEO and Chairman of the Board of Directors of Galapagos. "Frontier Medicines is a leading chemoproteomics company with a unique technology platform and a pipeline of potential best-in-class assets that fit with Galapagos' precision oncology R&D approach. The participation in Frontier Medicines' Series C round aligns with our innovation acceleration strategy to bring transformational medicines to patients around the world." Financing proceeds will support the advancement of multiple wholly-owned pipeline programs into clinical studies, including FMC-376. Frontier today announced the first participant dosed in the Phase 1/2 PROSPER clinical trial (NCT 06244771) evaluating FMC-376 in patients with KRASG12C cancers.

"Today we mark the first participant dosed with a therapeutic candidate born from the Frontier™ Platform, alongside a financing that affirms continued strong investor support. Frontier Medicines has amassed a robust data set that shows FMC-376 is expected to overcome the resistance seen with prior generation single-acting inhibitors, and we are excited to demonstrate this potential in the clinical setting."

Chris Varma
Chief Executive Officer
Frontier Medicines

Source: https://www.globenewswire.com/news-release/2024/02/22/2834057/0/en/Frontier-Medicines-Announces-Oversubscribed-80-Million-Series-C-Financing-to-Support-Progress-of-Clinical-Stage-Pipeline.html

ORI Capital Raises $260 Million

Press Release, February 22, 2024 (excerpt)

HONG KONG & NATICK, Mass.--(BUSINESS WIRE)--ORI Capital today announced the final close of its second fund, ORI Fund II (the “Fund”), with total commitments of $260 million. This milestone meets the Fund's original target and underscores strong investor confidence in ORI Capital’s investment strategy and track record.

Founded in 2015, and led by veteran investor, Simone Song, ORI Capital is well-positioned to identify and nurture the next generation of innovative companies. The Fund will invest in innovative early-stage biotech companies globally, across the areas of diagnostics, drug delivery, and therapeutics focused on areas of significant unmet medical need with the highest mortality rates such as cancer, metabolic disorders and neurodegenerative diseases. With a keen eye for transformative technologies and market trends, ORI Capital aims to drive value creation and sustainable growth for its portfolio companies.

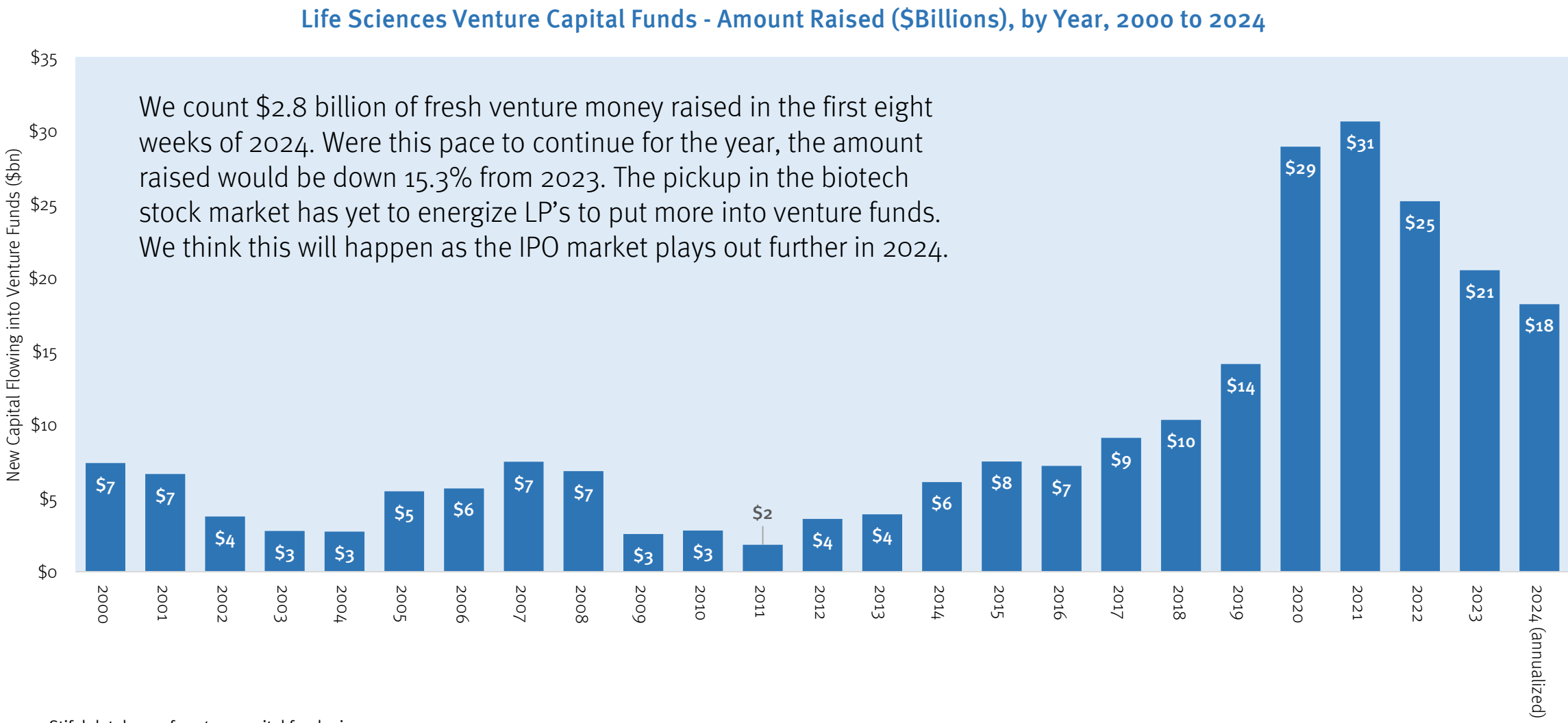
The ORI Capital investment team brings decades of experience investing in the biotech and healthcare sector and will leverage the expansive resources of the firm’s proprietary big data and AI-driven ORIZON platform to source differentiated investments and partner with companies to enhance value creation. ORI Capital is a pioneer in adopting a quantamental strategy in biotech venture investment combing data analysis with fundamental research.

“We are in a golden-era of innovation across the intersection of AI and biology, where technological breakthroughs are creating new approaches to diagnosing and treating disease,” said Simone Song, Founding Partner, ORI Capital. “We believe the current environment provides an attractive opportunity for investing in the next generation of leading biotech companies. Through our big data and AI-enabled ORIZON platform, we seek to be a capital provider of choice, to help founders and companies bring their innovative therapies and technologies to patients. We prioritize investments in companies tackling significant diseases with high mortality rates.”

ORI Capital’s strategy is focused on growth-oriented venture investments in biotech sector specifically targeting early to early to mid-stage life sciences companies developing novel therapeutics in addition to life sciences tools and diagnostics companies. Notable exits include: CG Oncology’s (NASDAQ:CGON) recent IPO on the NASDAQ which raised an double upsized offering of $380 million, Kymab which was acquired by Sanofi in January 2021 for $1.1 billion upfront, Semma Therapeutics which was acquired by Vertex in 2019 for $950 million in cash, as well as Orchard Therapeutics (NASDAQ:ORTX) and TriSalus Life Sciences (NASDAQ: TLSI) which both listed on the NASDAQ.

Source: https://www.businesswire.com/news/home/20240222384264/en/ORI-Capital-Raises-260-Million-for-Second-Life-Sciences-Fund

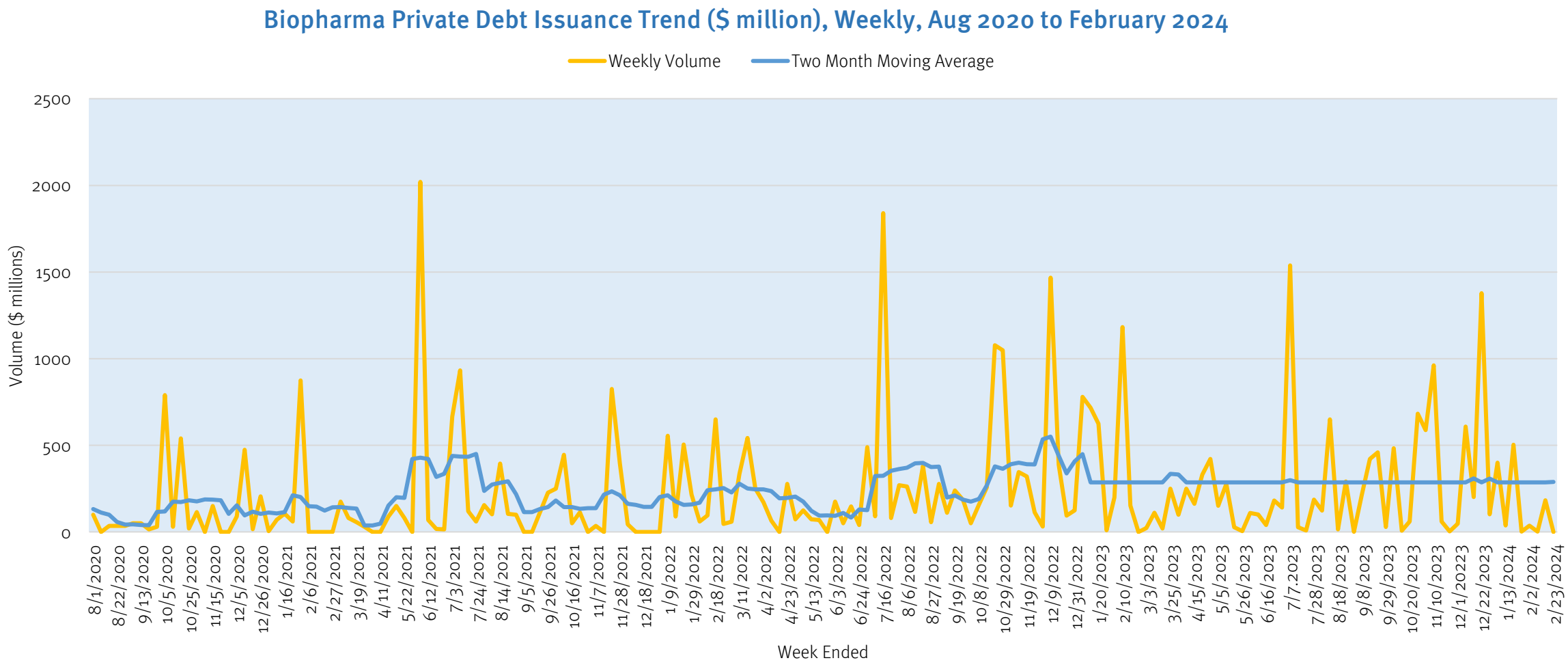
Pace of Life Sciences Venture Funds Inflow Down from 2023



Source: Stifel database of venture capital fund raises.

Biopharma Private Debt Placement Back in Business

The debt privates market was quiet last week with no major issuance taking place.

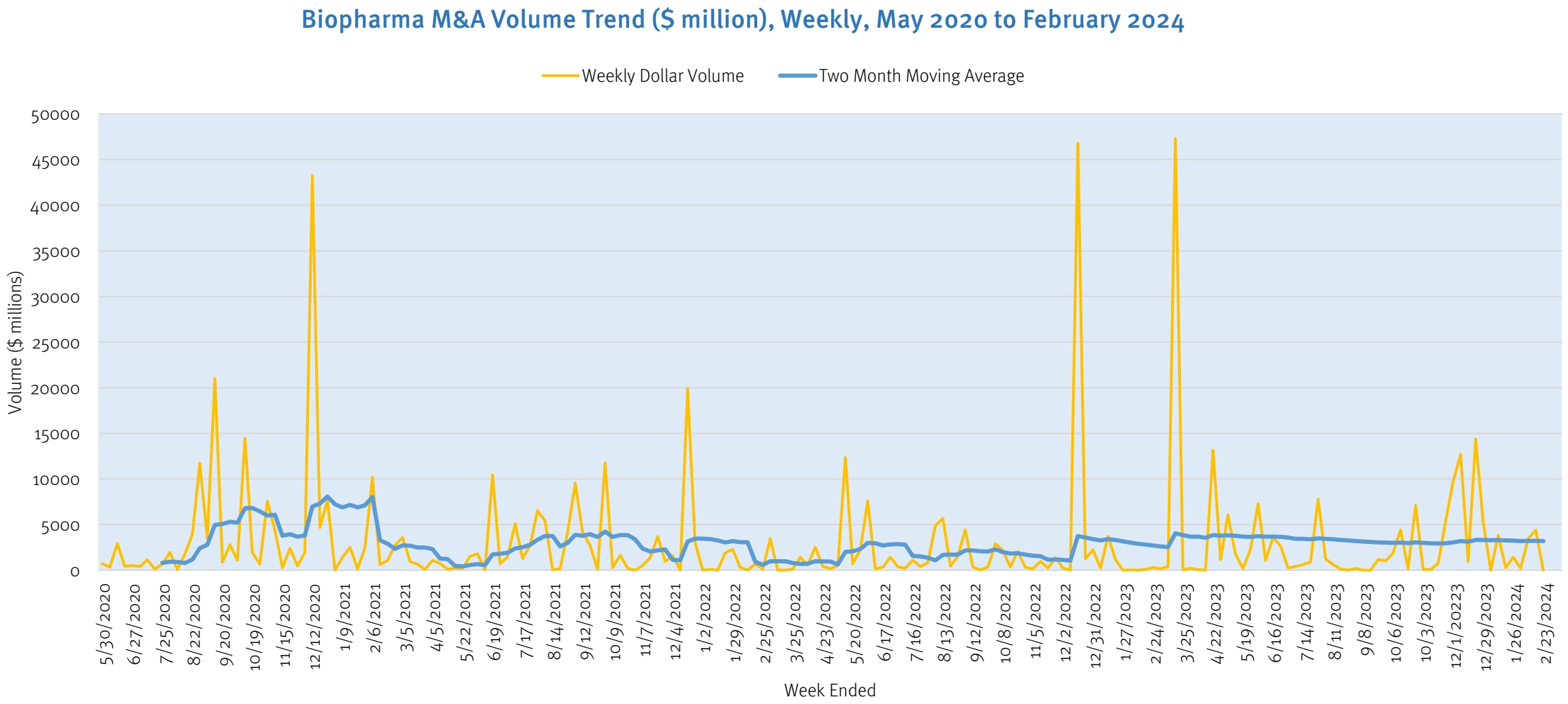


Source: Data from CapitalIQ, Crunchbase.

Deals Update

Last Week Saw No Meaningful M&A / Asset Sale Volume

Last week saw no meaningful M&A activity in the biopharma sector.



Source: S&P, CapitalIQ

Industry News

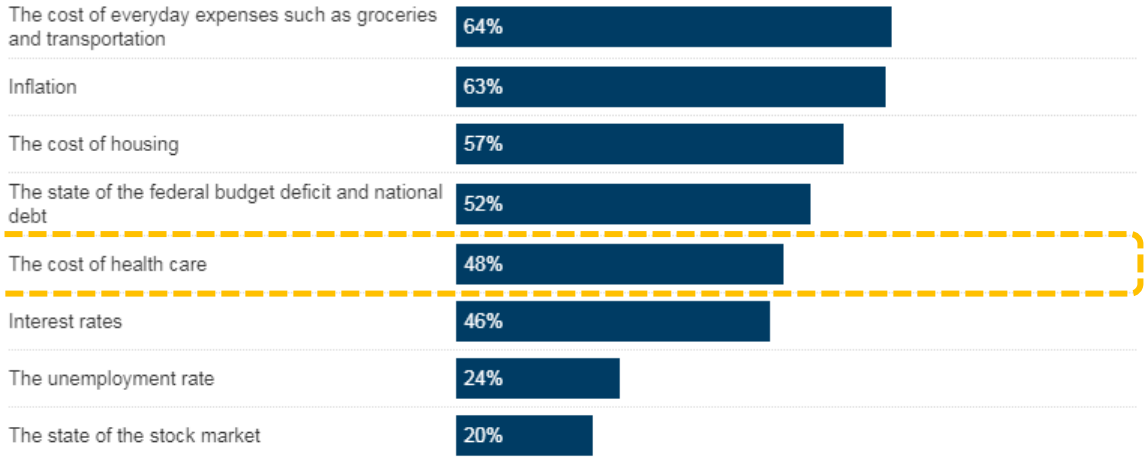
U.S. Voters Concerned About Healthcare Costs

Kaiser Family Foundation (KFF) Health Tracking Poll, February 21, 2024 (excerpt)

Figure 1

At Least Half Of Voters Say Inflation, Cost Of Everyday Expenses, Housing And Health Care Are Major Reasons They Describe Economy Negatively

Percent of voters who say each of the following is a **major reason** why they describe the condition of the national economy these days as "not so good" or "poor":



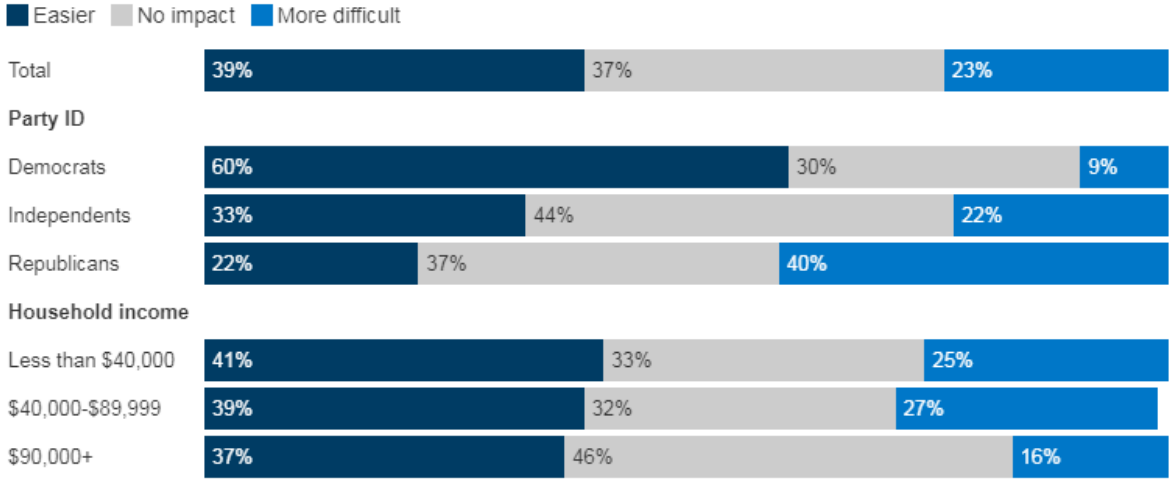
NOTE: Asked of those who describe the condition of the national economy as "not so good" or "poor." Percentages reported among total registered voters. See topline for full question wording.
SOURCE: KFF Health Tracking Poll (Jan. 30-Feb. 7, 2024) • PNG

KFF

Figure 10

Four In Ten Adults Say The ACA Has Made It Easier For People Like Them To Get Health Insurance, Including Similar Shares Across Household Income; Partisans Divide

Do you think the Affordable Care Act has made it easier for people like you to get health insurance, made it more difficult, or has it had no impact on the ability of people like you to get health insurance?



NOTE: See topline for full question wording.
SOURCE: KFF Health Tracking Poll (Jan. 30-Feb. 7, 2024) • PNG

KFF

Source: https://www.kff.org/affordable-care-act/poll-finding/kff-health-tracking-poll-february-2024-voters-on-two-key-health-care-issues-affordability-and-aca/

Biden or Trump: How Deeply Will 2024's Election Outcome Impact Pharma?

Michael Gibney, *Pharmavoice*, February 20, 2024 (excerpt)

November is a long way off, but the equally anticipated and dreaded 2024 U.S. presidential election has already hit a fever pitch. With nine months to go, the major parties' candidates appear set and the nation is off to the political races.

Between current president Joe Biden and former president Donald Trump, pharma companies find themselves between a rock and a hard place — both candidates have expressed an urge to reform the industry, although in different ways. And of course, voters are likely to respond to those desires on top of other pressing domestic and international concerns.

The Inflation Reduction Act has become one of the Biden administration's widest-reaching pieces of legislation, aiming to recover the economic losses during the pandemic and achieve some political goals along the way. One of those goals was to allow the agency that runs Medicare to negotiate drug prices with pharma companies.While the policy would potentially reduce drug costs for millions of older Americans, the pharma industry has fought hard against what it has collectively called a form of "price control."

For all intents and purposes, neither the pharma industry nor the Biden administration see themselves holding hands into the sunset. White House memos titled "President Biden Takes On Big Pharma and Is Lowering Prescription Drug Prices" don't paint the president as a friend to drugmakers. In that Feb. 1 notice, the administration blamed Big Pharma for "price gouging" and drew a line in the sand against the status quo of pharma price setting.

All said, a win for Biden in November could make changes to the IRA more difficult, and with drug prices a core tenet of his campaign, the pharma industry would likely remain in the crosshairs.

Trump's campaign has also rallied support around reducing drug costs even though he has spoken against the IRA for other reasons, including aspects addressing climate change, and members of the Republican party in Congress have called for a repeal of Medicare negotiation provisions.

During the twilight of his presidency, Trump issued an executive order referred to as the "most favored nation" proposal, which would have used international reference prices to lower drug costs in the U.S. Although the Centers for Medicare & Medicaid Services pulled the model, Trump's effort demonstrated that he, too, might look for ways to reduce drug costs in a second term, impacting pharma negatively — however, drug pricing has not been as central to his campaign this time around, according to reports.

One way Trump aimed to help lower prices was through free market competition and promoting biosimilars. By signing a law in 2018 that gave the FTC greater access to deals involving biosimilars, Trump signaled that expensive biologics like AbbVie's top-selling Humira could face more competition, and since the law passed, the approval of biosimilars overall has risen steadily.

Source: https://www.pharmavoice.com/news/biden-trump-2024-election-pharma-drug-prices/707846/

AbbVie Taps Longtime Executive Rob Michael as New CEO

Annika Kim Constantino, *CNBC*, Feb. 20, 2024 (excerpt)

AbbVie on Tuesday said longtime executive Robert Michael will become the company's new CEO, replacing Richard Gonzalez.

Michael, who is AbbVie's president and chief operating officer, will become the company's second-ever CEO on July 1. Gonzalez, who has led the company since it spun out from Abbott Laboratories in 2013, will retire and become AbbVie's executive chairman.

The announcement marks an end to Gonzalez's successful stint as the top executive of AbbVie, which transformed into one of the largest companies in the biotech and pharmaceutical industry in less than a decade.

It also comes as AbbVie grapples with one of the pharmaceutical industry's biggest losses of exclusivity, as its blockbuster autoimmune drug Humira faces fresh biosimilar competition. But the company is pinning its hopes on a pair of newer immunology drugs, Skyrizi and Rinvoq, to offset the losses from Humira.

AbbVie expects those two drugs to post $16 billion in sales this year and $27 billion by 2027, executives said during an earnings call earlier this month.

Rob Michael, AbbVie CEO Designate

Source: https://www.cnbc.com/2024/02/20/abbvie-taps-robert-michael-as-ceo-succeeding-richard-gonzalez.html

Emergent BioSolutions Names Joseph C. Papa As CEO

Mike Hollan, *PharmExec*, Feb. 22, 2024 (excerpt)

Joseph C. Papa is the new CEO of Emergent BioSolutions.

Papa will step into the role as of February 21, 2024, according to a press release from the company. He is taking over from interim CEO Haywood Miller.

Emergent Biosolution's lead product is the Narcan Nasal Spray, an over-the-counter opioid overdose treatment. In a press release, Papa said, “Whether it’s increasing access to Narcan® Nasal Spray, which is helping combat the opioid epidemic, or continuing to deliver important medical countermeasures to customers around the world, Emergent is providing critical products to address global health crises. I am confident that these important products provide for a bright future ahead as Emergent continues to lead in public health preparedness. I look forward to working with the team to accelerate the company’s progress, continue improving its financial position and drive value for shareholders. It is a privilege to join Emergent and chart a new chapter in this vital space.”

According to the press release, Papa will focus on returning the company to growth while also making moves to pay down the company’s debt. Prior to joining Emergent, Papa served as CEO at Bausch and Lomb Corporation, where he led the company’s IPO. At the time, the company was able to raise $630 million under Papa’s leadership.

Joe Papa, CEO, Emergent Biosolutions

Source: https://www.pharmexec.com/view/emergent-biosolutions-joseph-c-papa-ceo

Her Doctor Dismissed Her Extreme Morning Sickness. So She Found the Gene Behind It

Time, *Women of the Year Issue*, Feb. 21, 2024 (excerpt)

Fejzo, who is now 56 and a clinical assistant professor at the University of Southern California's Keck School of Medicine, had something more serious than typical morning sickness. She was ultimately diagnosed with hyperemesis gravidarum (HG), a condition that leads to extreme nausea and vomiting in 1% to 3% of pregnancies.

Haunted by her doctor's dismissal and the limits of his care, Fejzo tried to learn whatever she could about HG while she recovered. That turned out to be not much at all—the condition was barely studied at the time. (Many would only learn about HG when British royal Kate Middleton was hospitalized with it during her pregnancies.) "There was so little known," Fejzo says, but she had a hunch "there was something biological going on." She vowed to be the one to find out what it was, both for her own sake and that of her future children, twin daughters who were later born via surrogate. "I didn't want my daughters to have to go through that," she says. "Or anybody else."

Last year, more than two decades after her harrowing experience with HG, Fejzo had another breakthrough. In a paper published in Nature, she reported that people with HG tend to have high blood levels of GDF15 during pregnancy, yet produce lower-than-average amounts of GDF15 prior to pregnancy. When GDF15 levels naturally rise after conception, the shock to the system results in HG's relentless nausea and vomiting.

Dr. Marlena Fejzo, Time Woman of the Year

Source: https://time.com/collection/women-of-the-year/6691524/marlena-fejzo/

BioMarin Preaches Patience Amid Slow Sales for Hemophilia Gene Therapy

Ben Fidler, *Biopharma Dive*, Feb 23, 2024 (excerpt)

Roctavian's approval was a scientific milestone, the culmination of years of research developing a genetic medicine for the chronic blood disease hemophilia A.

Its launch, which began in Europe in 2022 and the U.S. last year, has been a focus for analysts and investors, many of whom viewed the product as a blockbuster-to-be. As a one-time, long-lasting treatment, Roctavian is billed as an alternative to the chronic therapies people with hemophilia A use to prevent bleeding.

Leerink Partners analysts once projected $2.2 billion in peak sales for Roctavian, and BioMarin was similarly optimistic, estimating in June the therapy would generate anywhere from $50 million to $150 million in 2023.

Yet so far, the drug is another cautionary tale of the challenges drugmakers can face selling a gene therapy. By November, BioMarin had slashed its revenue forecasts for 2023 to less than $10 million. And while Roctavian is included in BioMarin's $2.7 to $2.8 billion in expected sales in 2024, its contributions will be "relatively modest," said Chief Financial Officer Brian Mueller, on a conference call.

Multiple analysts cut their sales forecasts afterward. Leerink now expects about $1 billion in peak yearly sales, while Piper Sandler analyst Christopher Raymond projects $25 million, $31 million and $57 million, respectively, in sales each of the next three years.

Source: https://www.biopharmadive.com/news/biomarin-roctavian-sales-hemophilia-gene-therapy/708321/

It's mind boggling that Roctavian did only $3.5 million in sales last year while the Street pegged this as a $2bn+ drug.

IQVIA Institute Published “Global Trends in R&D” Last Week

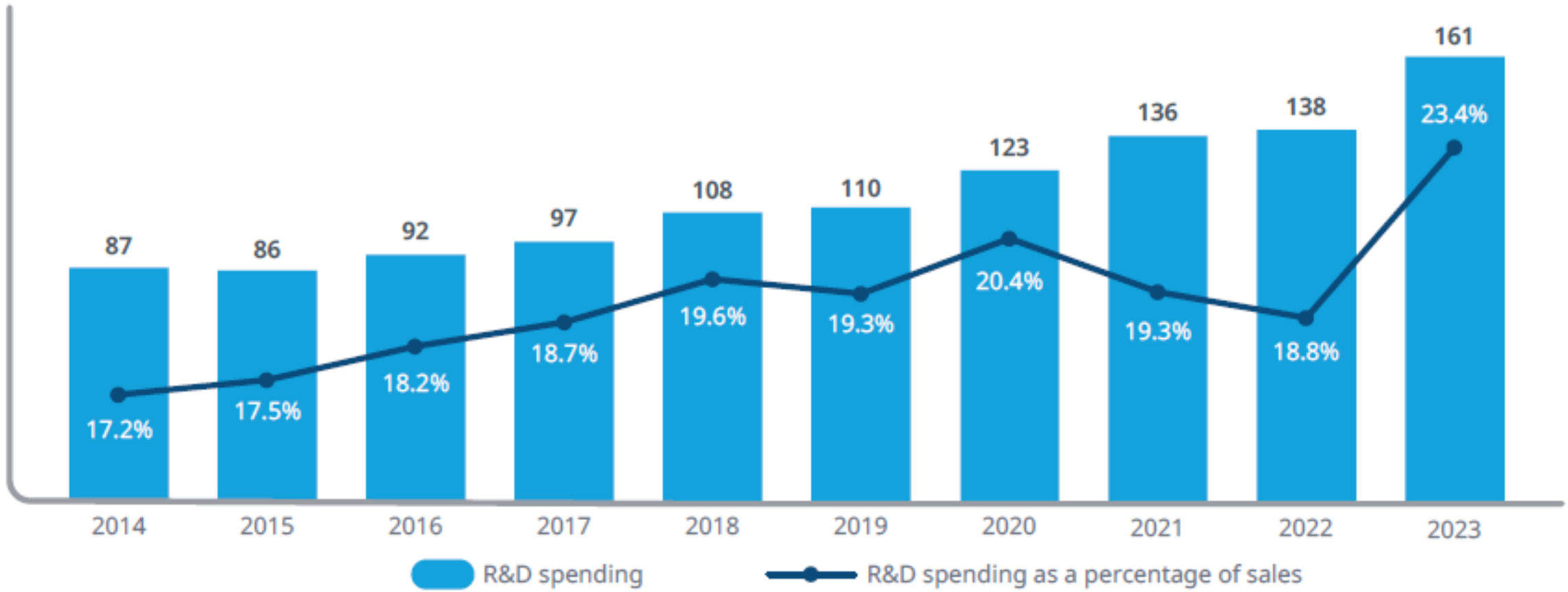
Key Findings

1. Clinical development productivity rose in 2023, primarily due to improvement in the composite success rate which jumped to 10.8%, the highest since 2018.
2. Industry and regulatory adoption of innovative and technology-driven enablers, including use of predictive biomarkers, novel trial design, and digital and decentralized trial methodologies contributed to productivity gains.
3. A total of 69 novel active substances (NASs) were launched globally in 2023, 6 more than the prior year, and including 24 first-in-class launches in the U.S.
4. Clinical development programs among larger biopharma companies are shifting away from areas such as COVID-19 and immuno-oncology to focus on hot spots in oncology and a range of therapies across large population and rare diseases.
5. R&D funding levels and deal activity reset in 2023 following a steep decline from peak levels in 2020-21.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

R&D expenditure by large pharma corporations totaled a record $161Bn in 2023, an increase of almost 50% since 2018

Exhibit 7: Large pharma R&D spending as a percentage of sales 2014–2023*, US$Bn

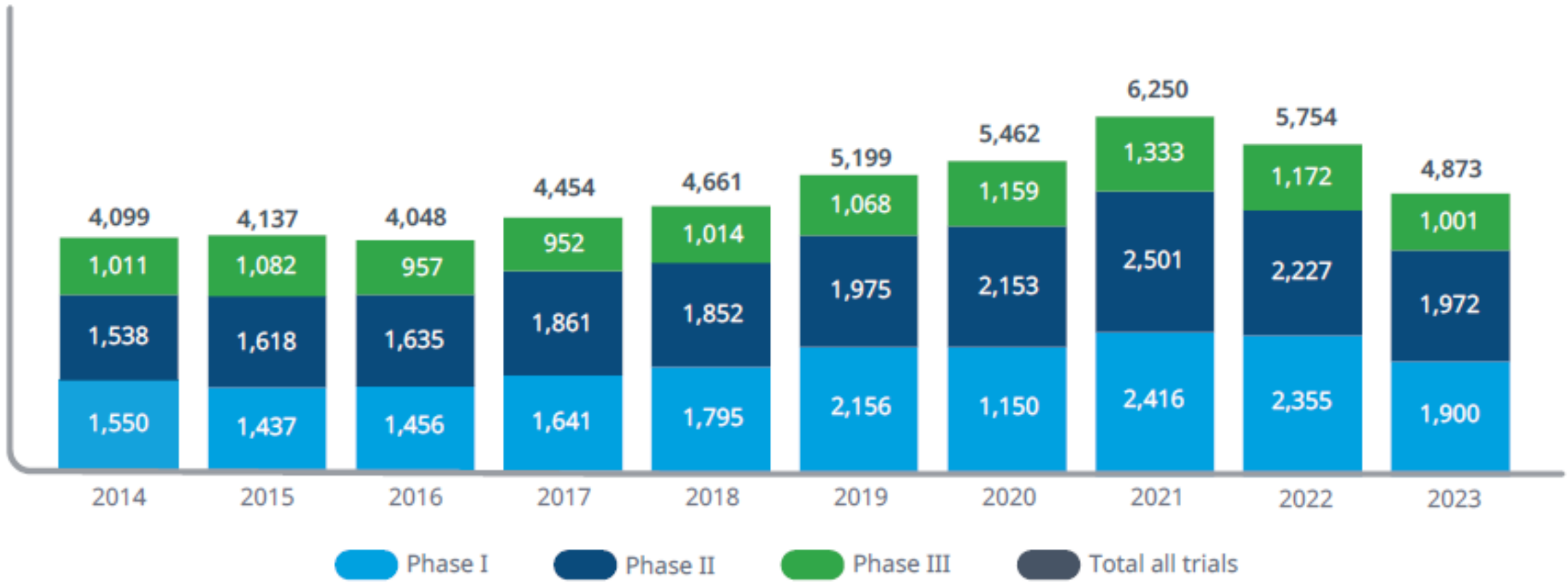


Source: Company financial statements, IQVIA Institute, Nov 2023.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Total clinical trial starts decreased by 15% in 2023, dipping below pre-pandemic level as COVID-19 trial starts slowed

Exhibit 8: Total number of clinical trial starts by phase, 2014–2023

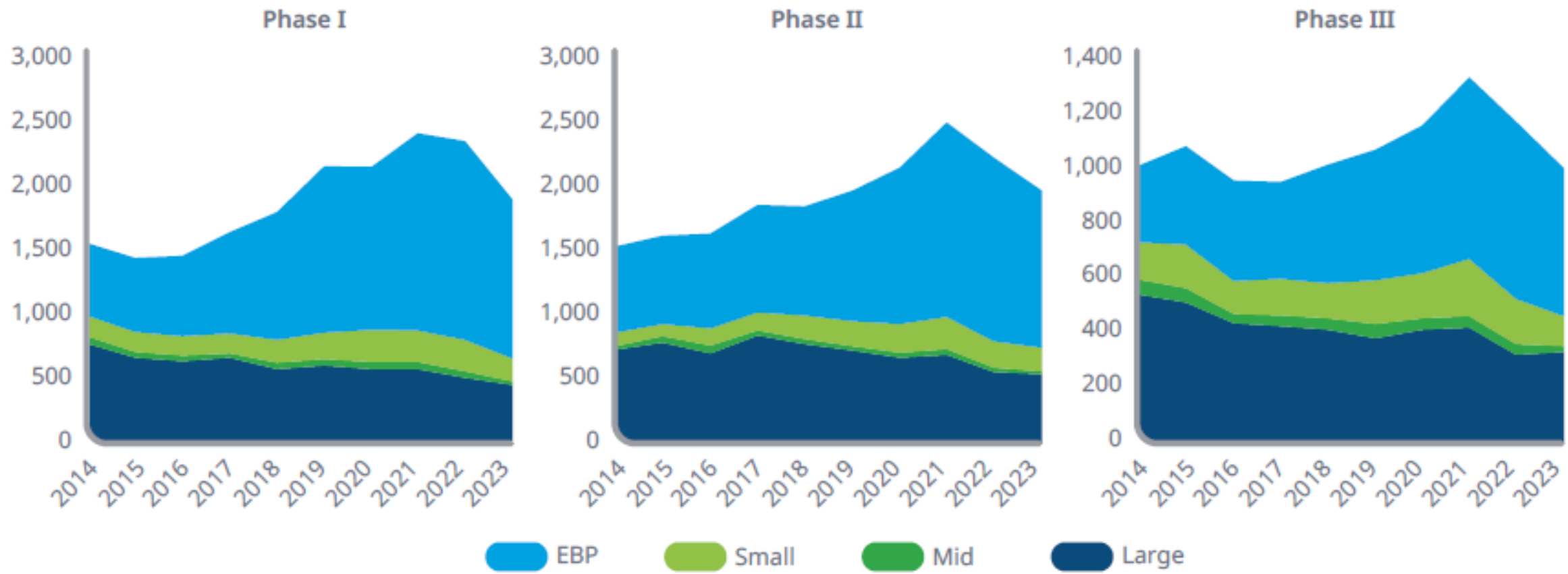


Source: Citeline Trialtrove, Jan 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Emerging biopharma companies are responsible for two-thirds of trial starts, but declined the most since the peak in 2021

Exhibit 10: Share of clinical trial starts by phase and company segment, 2014–2023

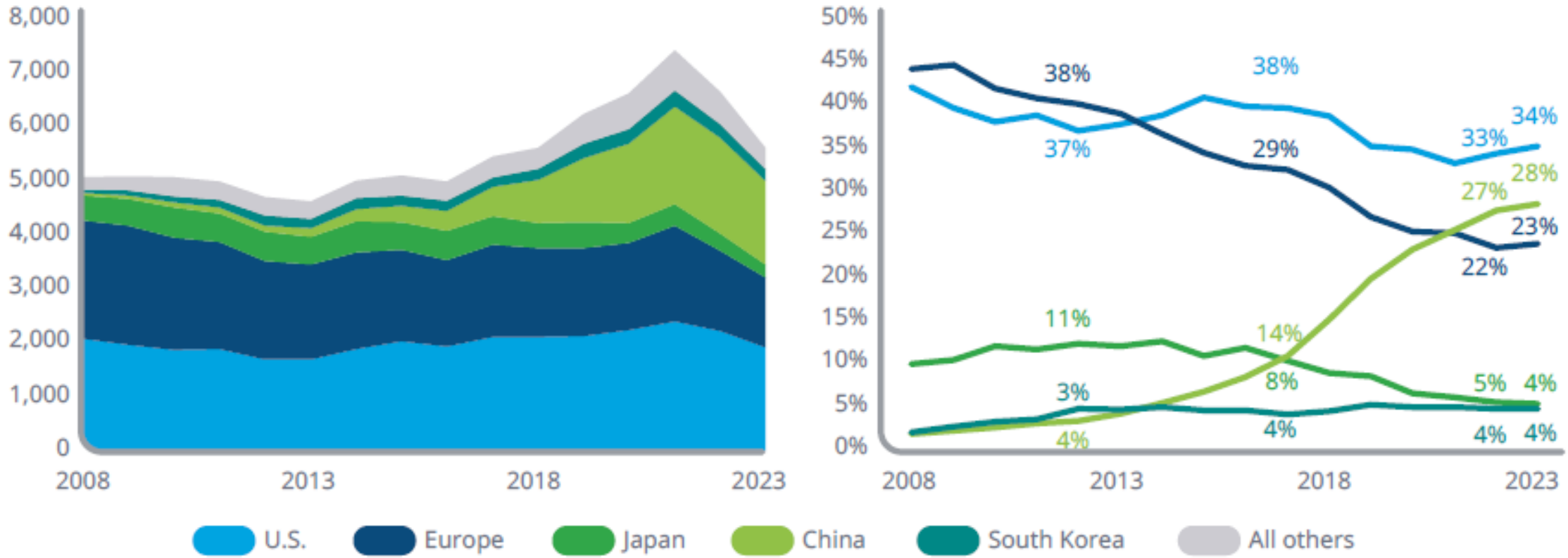


Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Trial starts from China-headquartered companies have risen to 28% of trial starts from 3% a decade ago

Exhibit 11: Number of Phase I to III trial starts based on company headquarters location, 2008–2023

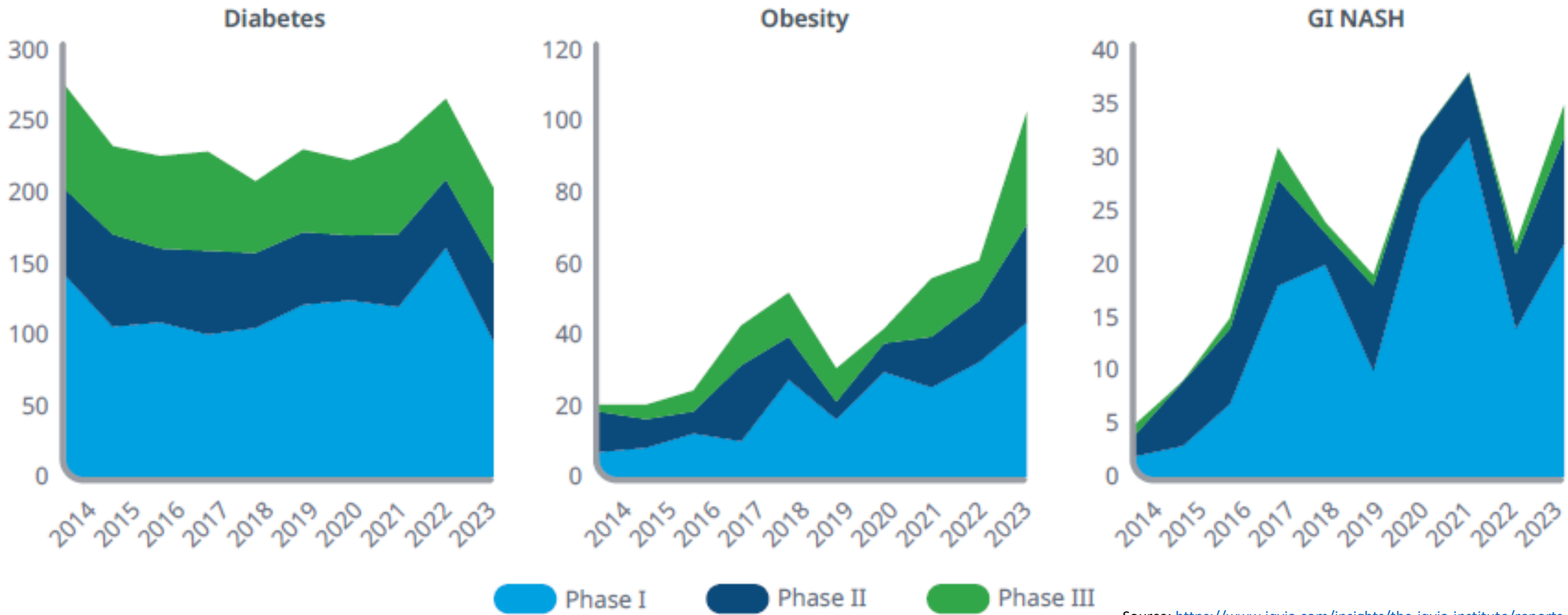


Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Obesity clinical trials in 2023 were up by 68% from 2022, and nearly doubled when compared to 5 years ago

Exhibit 19: Industry sponsored interventional trials by start date, 2014–2023



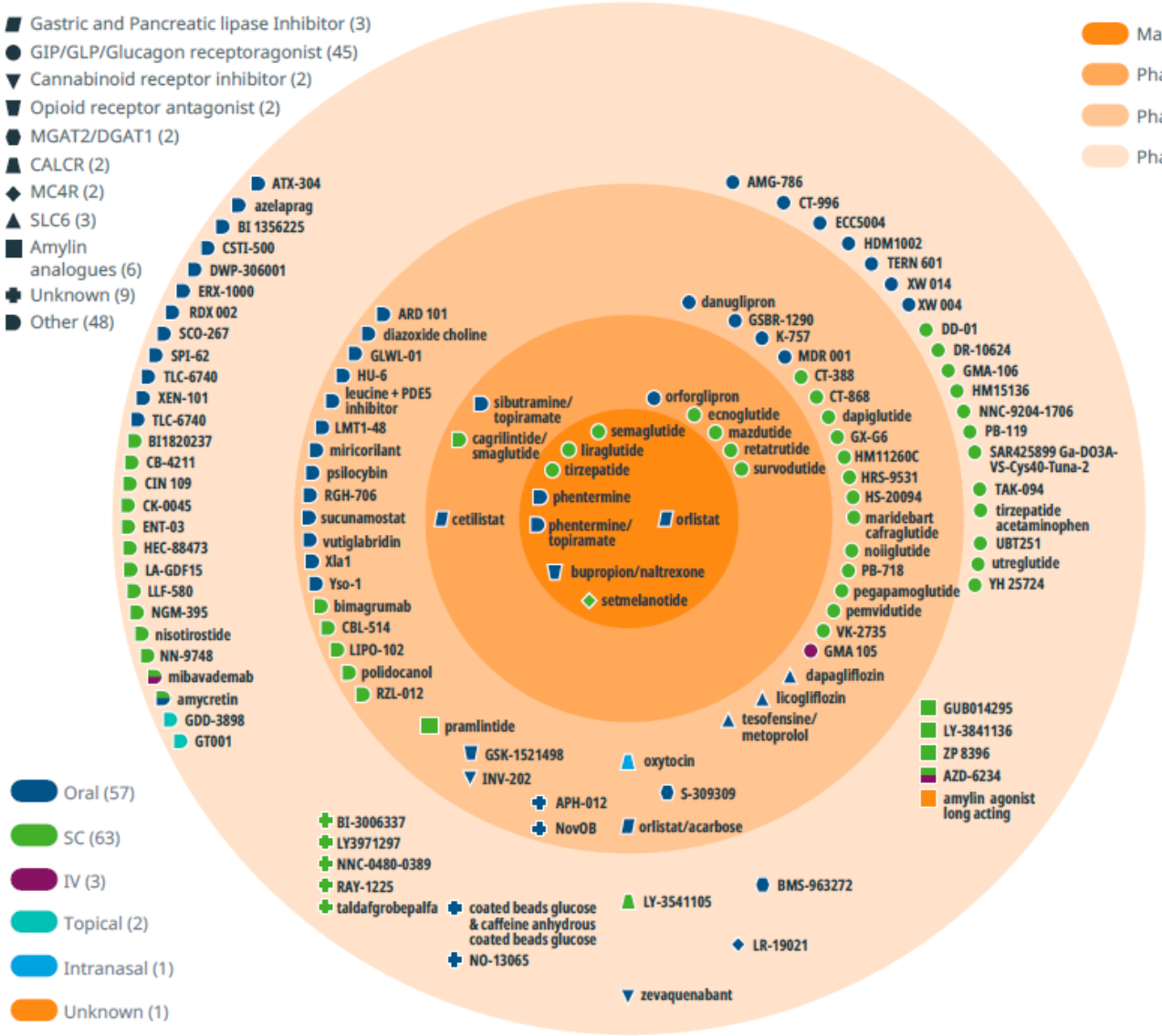
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Obesity Drug Pipeline Getting a Lot Bigger

With 124 drugs in development, over 35% drugs are GIP/GLP glucagon receptor agonists and 46% are orals

Exhibit 20: Obesity pipeline by phase, target and route of administration

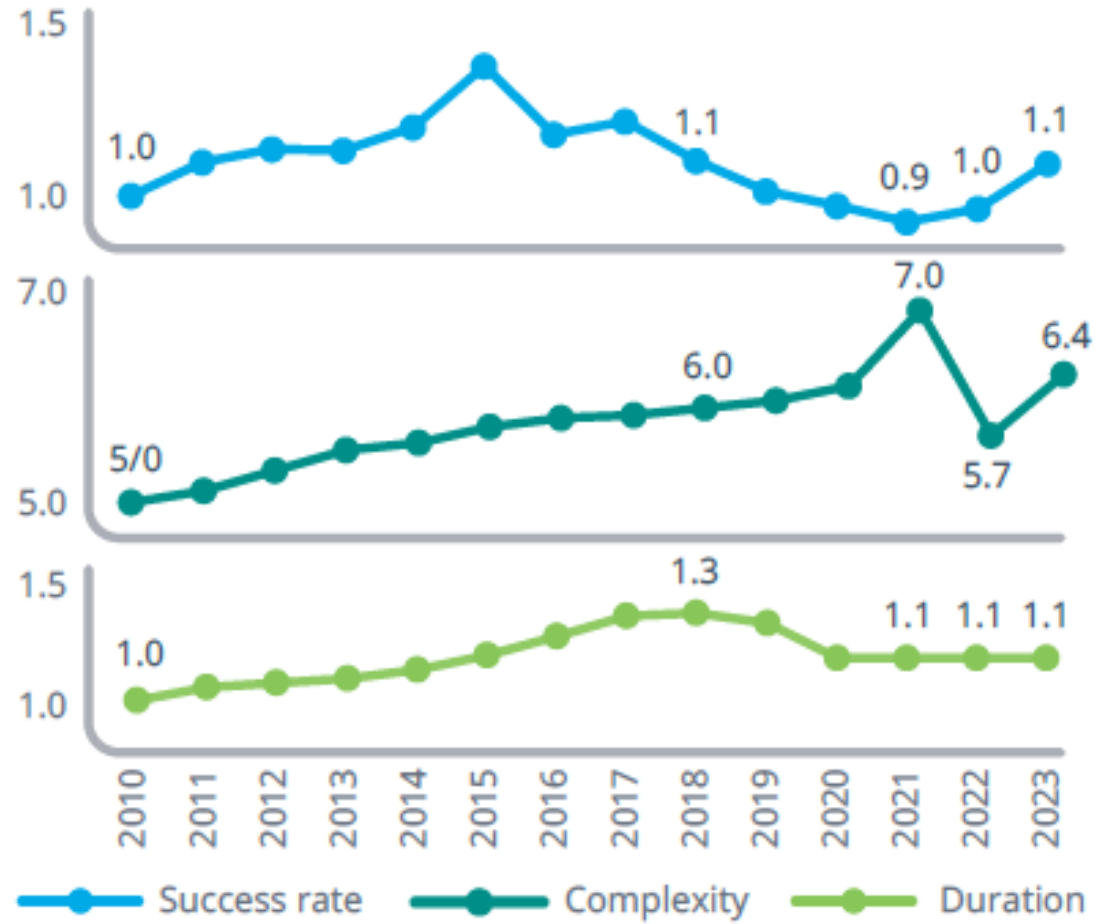


Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Clinical development productivity continued to increase in 2023 driven by an increase in success rates

Exhibit 34: Clinical Development Productivity Index and elements of productivity indexed to 2010 values



Source: IQVIA Pipeline Intelligence, Dec 2023; Citeline Trialtrove, IQVIA Institute, Jan 2024.

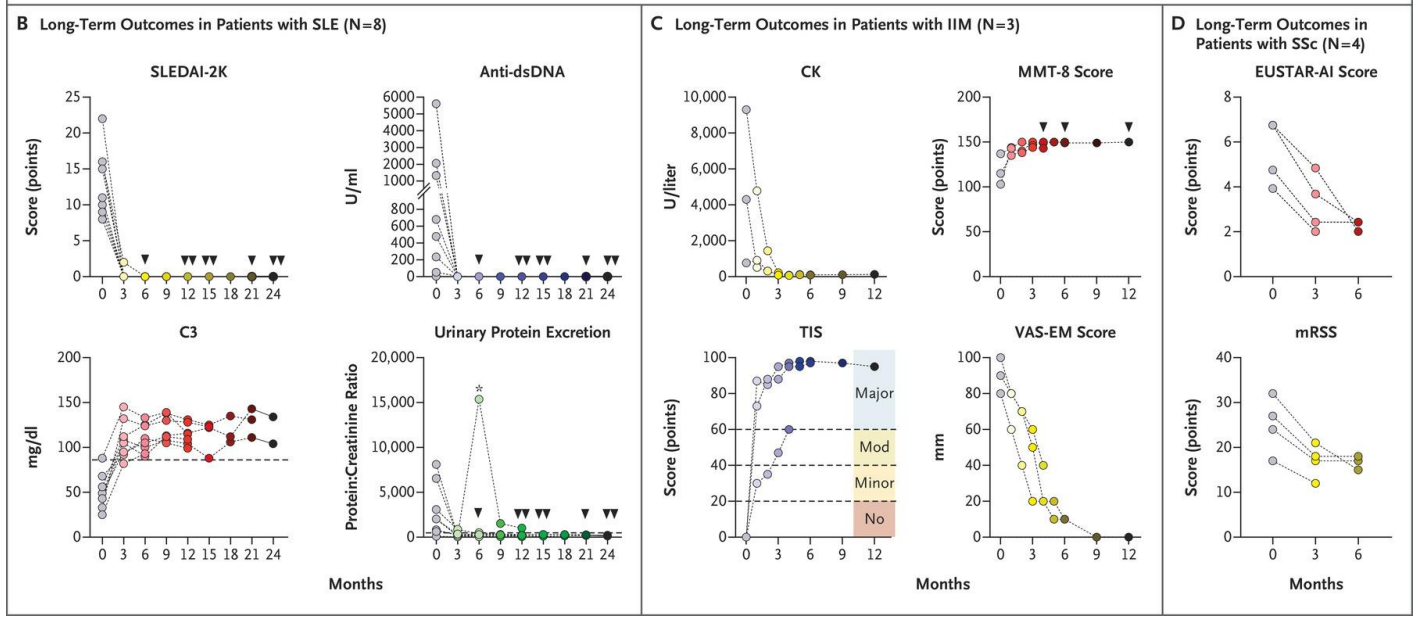
Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers

Stellar Schett Group / Cabaletta CD-19 CAR-T Long-Term Data Published Last Week in NEJM

Georg Schett and colleagues, "CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up," *New England Journal of Medicine*, Feb 22, 2024

A Short-Term Efficacy of CD19 CAR T-Cell Therapy in Autoimmune Disease

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE								IIM			SSc			
DORIS Remission	+	+	+	+	+	+	+	+*							
LLDAS	+	+	+	+	+	+	+	+*	N/A						
SLEDAI-2K Score	0	0	0	0	0	0	0	0				N/A			
ACR–EULAR Major Clinical Response									+	+	+*				
Normalization of CK Level									+	+	+*				
Change in EUSTAR-AI Score	N/A								N/A			−2.3	−4.7	−4.3	−1.9*
Change in mRSS												−7	−9	−17	−5*
Glucocorticoid-free State	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2308917

These data produced by George Schett and collaborators are remarkable, showing complete long-term remission of lupus and other autoimmune diseases with CAR-T therapy.

Prof. Dr. Georg Schett, Chair of Internal Medicine III, Erlangen,

Designer High-density Lipoprotein Particles Enhance Endothelial Barrier Function and Suppress Inflammation

Tim Hla and colleagues, Boston Childrens Hospital, *Science Signaling*, Feb 20, 2024 (excerpt)

High-density lipoprotein (HDL) nanoparticles promote endothelial cell (EC) function and suppress inflammation, but their utility in treating EC dysfunction has not been fully explored. Here, we describe a fusion protein named ApoA1-ApoM (A1M) consisting of apolipoprotein A1 (ApoA1), the principal structural protein of HDL that forms lipid nanoparticles, and ApoM, a chaperone for the bioactive lipid sphingosine 1-phosphate (S1P). A1M forms HDL-like particles, binds to S1P, and is signaling competent. Molecular dynamics simulations showed that the S1P-bound ApoM moiety in A1M efficiently activated EC surface receptors. Treatment of human umbilical vein ECs with A1M-S1P stimulated barrier function either alone or cooperatively with other barrier-enhancing molecules, including the stable prostacyclin analog iloprost, and suppressed cytokine-induced inflammation. A1M-S1P injection into mice during sterile inflammation suppressed neutrophil influx and inflammatory mediator secretion. Moreover, systemic A1M administration led to a sustained increase in circulating HDL-bound S1P and suppressed inflammation in a murine model of LPS-induced endotoxemia. We propose that A1M administration may enhance vascular endothelial barrier function, suppress cytokine storm, and promote resilience of the vascular endothelium.

Source: https://www.science.org/doi/10.1126/scisignal.adg9256

A fusion protein named ApoA1-ApoM was able to stabilize endothelial barrier function. This is an important finding because many diseases such as heart failure and AMD are caused, in part, by barrier dysfunction.

Dr. Tim Hla

Plasma Tau Test Matches/Beats Current CSF Alzheimer's Tests

Barthélemy, N.R., Salvadó, G., Schindler, S. et al. Highly Accurate Blood Test for Alzheimer's Disease Comparable or Superior to Clinical CSF Tests. *Nat Med* (2024).

With the emergence of Alzheimer's disease (AD) disease-modifying therapies, identifying patients who could benefit from these treatments becomes critical. We evaluated whether a precise blood test could perform as well as established cerebrospinal fluid (CSF) tests in detecting amyloid-β (Aβ) plaques and tau tangles. Plasma %p-tau217 (ratio of phosporylated-tau217 to non-phosphorylated tau) was analyzed by mass spectrometry in the Swedish BioFINDER-2 cohort (n=1,422) and the US Knight ADRC cohort (n=337). Matched CSF samples were analyzed with clinically used and FDA-approved automated immunoassays for Aβ42/40 and p-tau181/Aβ42. The primary and secondary outcomes were detection of brain Aβ or tau pathology, respectively, using PET imaging as the reference standard. Main analyses were focused on individuals with cognitive impairment (mild cognitive impairment and mild dementia), which is the target population for available disease-modifying treatments. Plasma %p-tau217 was clinically equivalent to FDA-approved CSF tests in classifying Aβ PET status, with an area-under-the-curve (AUC) for both between 0.95-0.97. Plasma %p-tau217 was generally superior to CSF tests in classification of tau-PET with AUCs of 0.95-0.98. In cognitively impaired sub-cohorts (BioFINDER-2: n=720; Knight ADRC: n=50), plasma %p-tau217 had an accuracy, positive predictive value and negative predictive value of 89-90% for Aβ PET and 87-88% for tau-PET status, which was clinically equivalent to CSF tests, further improving to 95% using a two cut-off approach.

This group of researchers led by Oskar Hansson (Lund) and Randy Bateman (Wash U) have undertaken a *tour de force* of work with mass spec to show that a relatively simple blood test could be used reliably to diagnose AD.

Randy Bateman (Wash U)

Source: https://www.nature.com/articles/s41591-024-02869-z. Photograph of Dr. Bateman (with Phil Needleman in background) taken by Tim Opler in January 2024.

Targeted Protein Degradation via Intramolecular Bivalent Glues

Hsia, O., Hinterndorfer, M., Cowan, A.D. et al. Targeted protein degradation via intramolecular bivalent glues. Nature (2024).

Targeted protein degradation is a pharmacological modality that is based on the induced proximity of an E3 ubiquitin ligase and a target protein to promote target ubiquitination and proteasomal degradation. This has been achieved either via proteolysis-targeting chimeras (PROTACs)—bifunctional compounds composed of two separate moieties that individually bind the target and E3 ligase, or via molecular glues that monovalently bind either the ligase or the target. Here, using orthogonal genetic screening, biophysical characterization and structural reconstitution, we investigate the mechanism of action of bifunctional degraders of BRD2 and BRD4, termed intramolecular bivalent glues (IBGs), and find that instead of connecting target and ligase in trans as PROTACs do, they simultaneously engage and connect two adjacent domains of the target protein in cis. This conformational change 'glues' BRD4 to the E3 ligases DCAF11 or DCAF16, leveraging intrinsic target–ligase affinities that do not translate to BRD4 degradation in the absence of compound. Structural insights into the ternary BRD4–IBG1–DCAF16 complex guided the rational design of improved degraders of low picomolar potency. We thus introduce a new modality in targeted protein degradation, which works by bridging protein domains in cis to enhance surface complementarity with E3 ligases for productive ubiquitination and degradation.

Source: https://www.nature.com/articles/s41586-024-07089-6

Current approaches to protein degradation typically involve two separate moieties that bind a target and E3 ligase (the key protein involved in protein disposal in degraders).

This paper published in *Nature* last week shows that it is also possible to degrade proteins with bifunctional degraders that change the conformation of binding proteins to enhance binding to E3 ligases.

The effect is to achieve much tighter binding to E3 ligase with what is termed a bivalent glue.

Biotech Value Creation Strategy

Disclaimer and Overview

These are slides that were shared with several generations of Summer interns in classes on how to think about biotech at Torreya Partners (prior to its acquisition by Stifel) in the 2012 to 2022 period. They were used particularly heavily during Zoom sessions held for countless interns during the Covid-19 Pandemic. You'll note that the slides have a certain timebound frame of reference.

A number of those interns have gone on to successful positions in the pharma industry, the buyside or the sellside. And a number have become successful company founders.

Even though you might find much of the material to be a bit remedial or basic we thought there might be some points of interest for those focused on value-creation strategies in biotech.

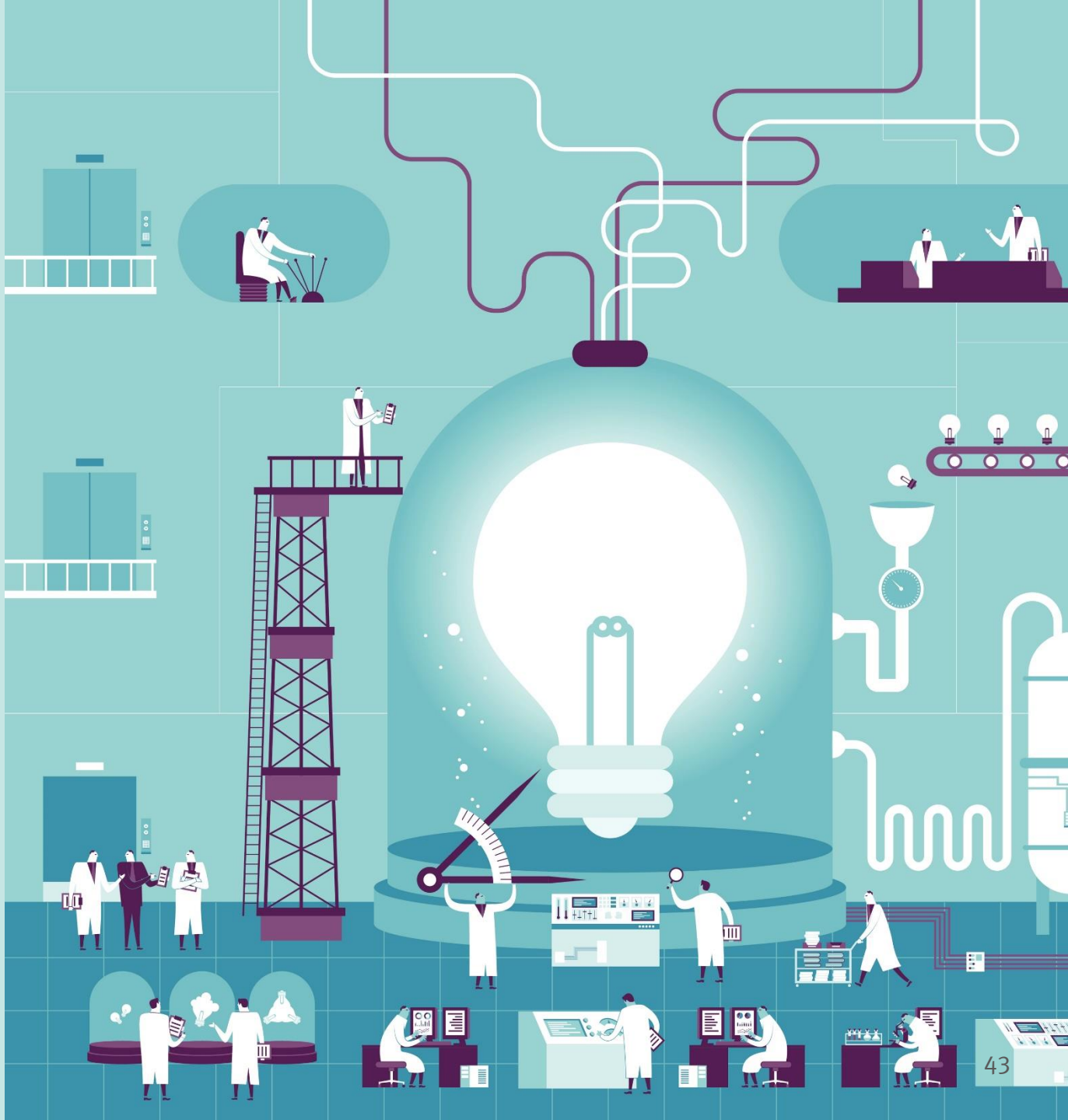
These slides express points of view on biotech strategy that are those of the author (Tim Opler) and not necessarily those held by others at Stifel.

Building and Running a Good Biotech is Really Hard

A biotech company seeks to develop therapeutics to treat disease and is engaged in drug R&D. This can be done by licensing intellectual property from an inventor or, instead, by inventing molecules from scratch.

Every company has to start somewhere, and entrepreneurs or incubators will typically create a biotech company from scratch. Starting a biotech company is not that hard. It's done every day by university students and professors, entrepreneurs, venture formation organizations and, even, hedge funds.

Building a really good biotech company, on the other hand, can be quite hard. This involves matching a good idea to appropriate resources to achieve value for investors and for patients. This will typically require a deep understanding of technologies, competition and financial markets. This section discusses some of the relevant factors to consider.



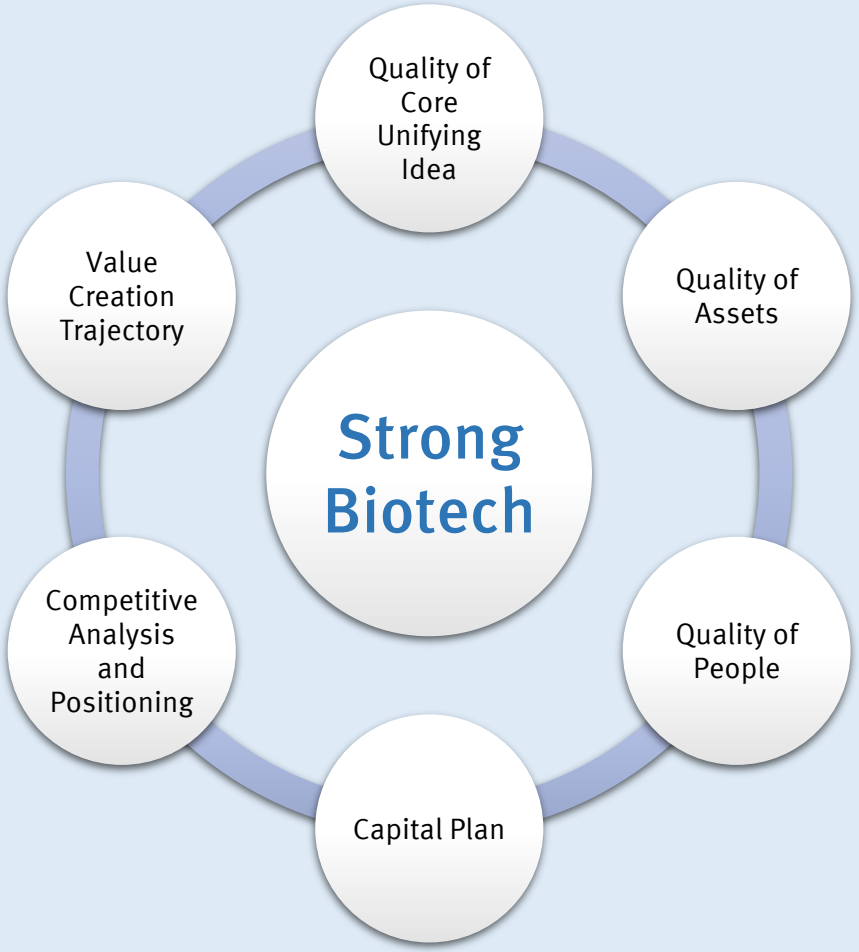
There are Six Elements of Biotech Strategy

A good biotech company calls for a great idea.

This idea can come from anywhere. An insight into an unmet patient need perhaps.

Or a technology discovery. Or an accidental finding that leads to an insight into an opportunity for helping patients.

Once the idea is in place, assets will have to be licensed, purchased or created. One will need to hire appropriate people. Raise the requisite money. One will need to then execute off a business blueprint (called a business plan) which will set a value trajectory. It's important to recognize not just where the competition is today, but where it's going to be when your drug nears its point of approval.



Biotech Asset Finding Involves Getting Into a Groove

You get an idea. Hopefully off the beaten path. Find some researchers. Read their work on Pubmed. Get familiar. Then hit their patents. Look at pharma assets in an area. Is there some patent estate around? Use Google to look for competitive programs and related ideas. Particularly look for ways to **reposition assets**. This is an iterative process. At some point you end up with a stack of thirty or so papers and a bunch of thinking from the research community. Some of it will be wrong and some of it will deeply insightful and brilliant. You have to find the **signal in the noise**. The innovative idea that can be translated into a medicine for people who really need it. It will often be important to pull together disparate ideas and sources to see a novel opportunity for a biotech asset.

The Valley of Death

The term “Valley of Death” (VOD) has come to describe the period of transition when a developing technology is deemed promising, but too early stage to validate its commercial potential and thereby attract the capital necessary for its continued development. During this transition, there is often a funding gap due to the wariness of risk-averse investors. Entrepreneurs in biotech live in fear of getting caught in this “Valley of Death”.

If you ever want to see what the VOD looks like go to a conference that promises to introduce you to family office investors for a fee. There are a number of groups who run such conferences, telling capital-starved biotechs that they just need to meet the right families. Mythical rich people who love early-stage science. This would be better called the “Valley of Folly.” Just give us your money or buy this website subscription and we will get you to the nice people waiting to give you their money.

The essence of designing a biotech business plan is to never get anywhere close to the VOD.

This is not to say you don’t have to work to raise money. It’s really hard work. We’re just saying you should never be caught without it. A biotech business plan has to be either pre-funded or fundable at all points in its lifecycle. If you are running a biotech and find yourself in the VOD you may not have thought through your business plan well enough at the beginning.

Experts on Designing Biotech Business Strategies

A key idea is to efficiently get to a signal of drug efficacy. Ideally, that signal would be really strong.

Mary Lynne Hedley
Fellow, Broad Institute

- Led TESARO as President into its sale to GSK.
- Was CSO at Abraxis and MGI PHARMA.
- Holds Ph.D. from UT Southwestern.

Mary Lynn Hedley

Hedley is all about early signal generation in drug discovery. She has said that the key to drug discovery is to run an early study that will allow you to show that your drug works well for a specific set of patients. If done right, this study should never cost more than $5 million. Hedley worked effectively with partner, Lonnie Moulder, to build up and exit multiple pharmas in oncology around the principle of efficiency in development.

Josh Bilenker
Founder, Loxo Oncology

- Led Loxo as CEO through its sale to Lilly
- Runs Treeline Biosciences today
- Was an investor at Aisling
- Previously at FDA
- MD, Johns Hopkins

Josh Bilenker

Bilenker has done well by promoting the idea that it's much better to show high efficacy in a narrow genetically preselected population of cancer patients than so-so efficacy in a broad population. His latest company, Treeline, is developing NCE's in oncology.

Phil Needleman: the Ultimate Drug Developer

Lessons Learned in Industry

Philip Needleman, M.D.
Former Head R&D, Pharmacia

From Bruce Booth's Blog Post on Needleman's Ten Commandments:

"Phenomenology is very different than pharmacology". Phil's admonition is to only take drugs into patients where you know the mechanism of action and can therefore optimize the drug's SAR rationally.

"Define and do the killer experiments". "you need ice in your veins – if a killer experiment doesn't work then kill the program".

"Find the shortest route to heaven". In discovery, don't spend years doing every preclinical pharmacology model – do a few, not half-a-dozen or more – and then with confidence sprint quickly to the drug's PoC in patients. In the clinic, if you need to focus on a limited-use first, go for it and get approved with a narrow label fast, even over the cries of your commercial colleagues.

"I'm from Missouri… show me data". As he says, "the coinage of the realm is data" so spare the hand-waving talk, wordy powerpoints, and show the data, "gleamed both at the bench but also occasionally in hard-nosed reviews with experts". Needleman loves the great Edwards Deming quote: *"In god we trust, all others must bring data".*

Source: https://lifescivc.com/2013/03/phil-needlemans-ten-commandments-of-drug-rd/

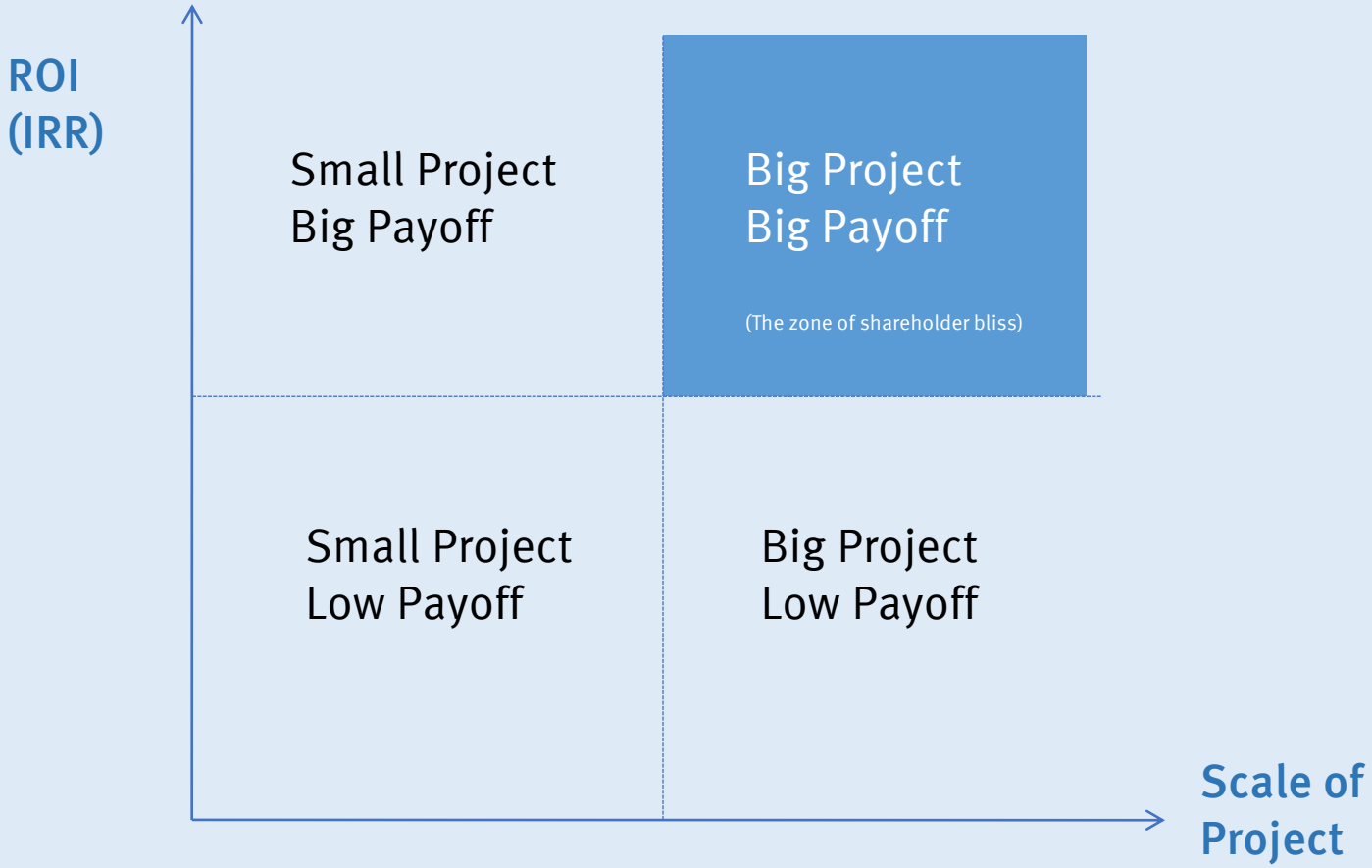
Building Value: Think Big And Run the Numbers

- Value building comes from assets with NPV that is well above cost.
- At the extreme, one can simply acquire assets with very high ROI.
- ROI = NPV / price paid (or, with more complexity, internal rate of return (IRR) – the discount rate that sets NPV to zero).
- This can lead to strangely configured portfolios. One can imagine 10 companies under a holdco that have completely different business purposes.
- We emphasize several finance points in considering value creation:
    1. Go **big**. It's NPV. Not IRR. **Better to try to create a billion-dollar product than ten hundred-million-dollar products.** Or, these days, try to create a $100 billion product.
    2. Check your NPV's with comparables. The stock market will determine how much capital you can raise, not your spreadsheet. We like to use market comparables to determine value creation.
    3. We have developed a comparables approach that is akin to the film "Moneyball". The idea is to map biotech attributes to value in the market. More at the end of this section on this topic.

"Successful companies create value by providing products or services their customers value more highly than available alternatives. They do this while consuming fewer resources, leaving more resources available to satisfy other needs in society. Value creation involves making people's lives better. It is contributing to prosperity in society."

Charles Koch

Building Value: You Want to Scale Up a High ROI Project



The key to creating lasting value is to bet big and win.

If you play your cards right, you can find a project with a high ROI and substantial scale.*

Another key opportunity is work with a technology or project that opens up numerous other opportunities to create value (an accordion project).

* Also see the interview last week with Bob Nelsen of Arch Venture by *BioCentury* (https://www.youtube.com/watch?v=OJPAOQdErio).

Building Value: Registrational Strategy is Not Business Strategy

Most biotech CEOs figure out what it will take to get an idea to FDA or EMA approval and set out to do it. The thinking is you just fight hard enough, and you'll get there somehow. Eventually.

- Maybe its two Phase 3 studies that show that your new pain drug is effective.
- You run your way through Phase 1 and Phase 2 as quickly as possible to get to the Phase 3's.

This approach misses how the game is played. **It's not registration that you should focus on first. Rather, it's convincing investors to give you the money to get your drug to registration.** The FDA is not the customer you are trying to satisfy. It's the investor.

- What you want to do is run the study that allows you to fund the program to registration.
    - The only time to run Phase 3 studies is when you know they are going to work.
    - Losing tens of millions of dollars in Phase 3 is an unforgivable mistake. You waste money that could have been used to serve patients otherwise.
- That is, you need data out of your early clinical study that convinces that you have an active drug candidate:
    - You need to get investors excited about the potential of the project with data.
    - If you do it right, investors will give you a mandate to go forward and take your drug to the market.
- More or less, investors follow Bayes' Theorem:
    - Given a dataset what is the probability of FDA approval?
    - If the probability is high and your market is big, your valuation will be high. If your valuation is high, you can raise all the money you need. You can run registrational Phase 3 studies all day.
- **Basically, early drug development is a *business* exercise; not a *clinical* exercise. Biotech access to resources is highly constrained and must be earned through displaying strong efficacy datasets to the market.**

A common biotech mistake is failing to design strategies that allow a company to fund itself to registration.

Most simply chase the registration without contemplating what investors need to see first.

Building Value: Organizations / Leadership

It's important to build a biotech organization that can execute, be flexible and do its own thinking.

Value is created by *organizations* rather than by brilliant individuals:

- Key to have an organization with capabilities that match the task at hand.
- Each person in an organization needs to be well-suited to their role and resourced to get their job done.
- Most companies start by saying this is what we are good at and, therefore define their strategy accordingly.
- One could easily imagine this leading to a very good "horse and buggy" manufacturer.
- Much more important to look at the environment and imagine the medicines that society will want to pay for and build them ahead of time. Then build the organization to get there.
- A good organization tends to have a strong leader who can help to referee resource allocation debates and lead the company in the direction of those decisions which maximize value.
- A good organization can evolve and shift completely in its approach to the market and its mindset. These organizations tend to have top teams who are empowered and middle-management who work in synch to get things done.*
- Organizations can also have "playbooks" where they follow heuristics in the value-creation process. They might have special insight into what to do with AI, RNA editing or cellular reprogramming, for example.

"We are building a special capability at Schering-Plough to respond to these and other challenges with innovation, speed and flexibility. We aspire to continue being the company delivering the most positive change of any in our peer group, as we work to deliver our Turnaround and advance our six- to eight-year Action Agenda for transformational change."

Fred Hassan*

(Fmr. CEO, Pharmacia & Schering-Plough)

* See Fred Hassan, *ReInvent,* 2013 (https://www.amazon.com/Reinvent-Leaders-Playbook-Serial-Success/dp/1118529855), https://chiefexecutive.net/amplify-your-bandwidth-the-present-gen-ceo-playbook/ (2024) and https://soundcloud.com/vanguardnetwork/knowing-who-you-are-not-with-fred-hassan-and-tal-zaks (2024).

Quotes on Biotech Leadership

“If you want an innovative environment, hire innovative people, listen to them tell you what they want, and do it.”

Arthur D. Levinson, CEO, Genentech

“If you’re working on a problem you deeply care about, you would rather focus on something epically important and fail. So, I think the more important the idea, the better chance of changing people’s lives if you’re successful, the easier it is to attract amazing people, and the ball is rolling.”

Hans Bishop, CEO, Juno

“Integrity, insight and inclusiveness are the three essential qualities of leadership.

Sadhguru

“A leader is best when people barely know he exists, when his work is done, his aim fulfilled, they will say: we did it ourselves.”

Lao Tzu

Building Value: Be Unafraid of Oddball Ideas

Go where others don't dare to go

Teva to Acquire Cephalon in $6.8 Billion Transaction

- Enhances and Diversifies Teva's Branded Portfolio
- Pipeline and Marketed Products Broaden Reach into Key Therapeutic Areas Including CNS, Oncology, Respiratory and Pain Management
- Attractive Economics with at Least $500 Million in Cost Synergies
- Accretive to non-GAAP Earnings Immediately; Accretive to GAAP Earnings Within Fourth Quarter of Closing
- Companies to Host Conference Call at 8:30 AM ET

May 02, 2011 07:00 AM Eastern Daylight Time

JERUSALEM & FRAZER, Pa.--(BUSINESS WIRE)--Teva Pharmaceutical Industries Ltd. (NASDAQ: TEVA) and Cephalon, Inc. (NASDAQ: CEPH) today announced that their Boards of Directors have unanimously approved a definitive agreement under which Teva will acquire all of the outstanding shares of Cephalon for $81.50 per share in cash, or a total enterprise value of approximately $6.8 billion. The transaction is not conditioned on financing and is expected to be completed in the third quarter of 2011.

Frank Baldino, Jr.

Founded Cephalon in 1987. Died in 2010.

Completely opportunistic in asset acquisitions. Found weird ideas like Provigil® from Groupe Lafon. This was to keep people awake.

The company did many acquisitions of "oddball" assets that defined new therapeutic categories.

Baldino teaches us to look where others don't go. If everyone else is looking for better KRAS inhibitors, then go look at something no one has ever heard of. You need to find the place where the asset market is inefficient, and you may be able to buy a very good asset for a reasonable price. Better to be opportunistic than religious about therapeutic areas or other categories. This sounds easy, like something everyone is doing, but you have to do the work to get this to happen and be willing to kill almost all ideas you run into.

Building Value: Do The Work

And build deep teams that know how to do the work

There is *no rulebook* for value creation:

- Incredibly important to have an open mind when seeing new opportunities
- We find most companies that we interact with have incredibly strong *biases*. That is, people enter drug discussions with strong prior beliefs that shape views.
- Our experience is that scientists (theoretically, evidence-based people) tend to be the most biased. An experienced scientist will bring decades of experience and will find all sorts of reasons to rule out high payoff ideas.
- It's very important for each of us to learn to "step outside of ourselves".
- The best companies create an internal discipline and process to avoid biases and Groupthink.
- Very important to *do the work* on an asset. That is, do not knock out an asset because of a view that one has regarding its MOA etc.
- The best companies create teams that are *deep enough* to support doing the work.

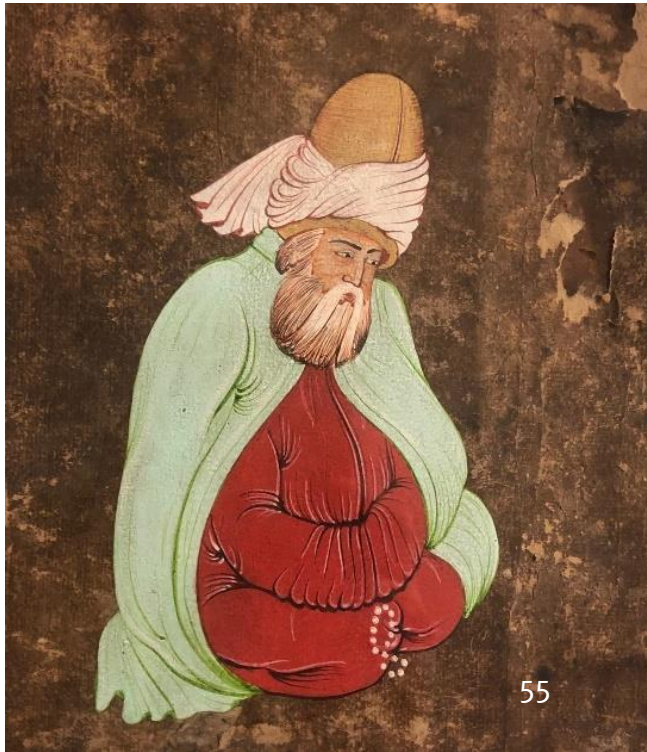
Time horizon:

- In general, long-term value creation can be created with R&D based strategies.
- Shorter-term value creation will only be possible from business development driven strategies.
- But even great business development deals take a long-time to turn into real value.

"Imitating others, I failed to find myself. I looked inside and discovered I only knew my name. When I stepped outside I found my real Self."

~Rumi

(13th century Persian poet)



Quotes on Doing the Work

“One of the things I've learned over the years is not to be scared of hard.”
Mike Gilman, CEO, Arrakis

“Successful innovation is not a feat of intellect, but of will.”
Joseph Schumpeter, Austrian Economist

“It’s difficult to see the picture when you’re inside the frame.”
Eugene Kleiner

"Clearly, there are easier and less insane ways to make a living.“
Jim Greenwood, former CEO, BIO (on being a biotech CEO)

“The rewards for biotechnology are tremendous - to solve disease, eliminate poverty, age gracefully. It sounds so much cooler than Facebook.”
George M. Church

“Success is the ability to go from one failure to another with no loss of enthusiasm.”
Winston Churchill

“Ideas are easy. Execution is everything. It takes a team to win.”
John Doerr

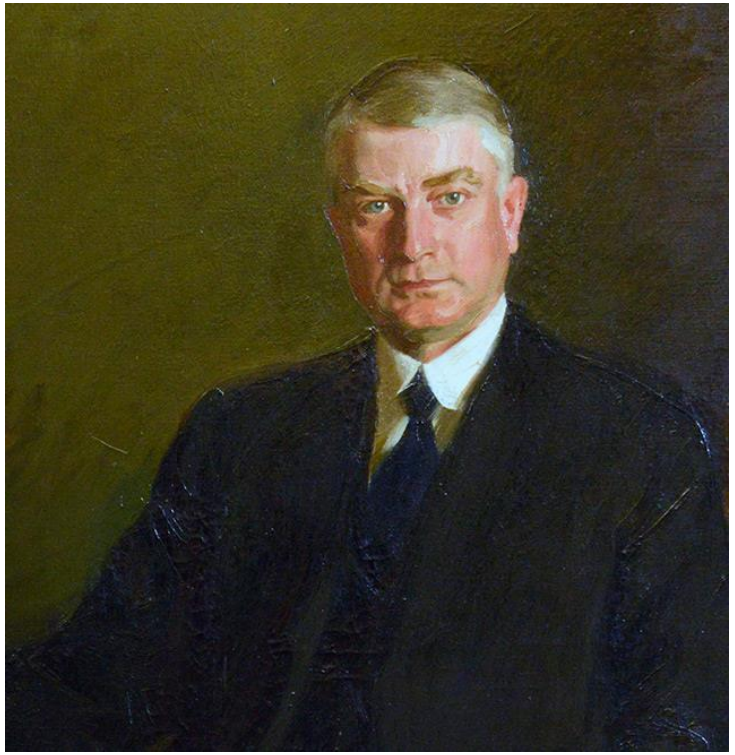
“Just because you can doesn’t mean you should.”
Sherrilyn Kenyon

Building Value: Imagination Key

We once had lunch we had once with a pharma executive in 2002 who complained that all the good ideas had already been turned into drugs and that there wasn't that much left to do.

Obviously, one needs to have a little imagination to think about what might be possible. To quote Will Mayo, an early ambassador of the medical profession, one needs to "look through a half-opened door into the future, full of interest, intriguing beyond my power to describe…"

Imagination, the ability to envision a yet unseen opportunity, again and again has been the critical success factor behind IP-intensive industries. This imagination typically emerges from a thorough understanding of current technologies and a sense of what is possible with novel technologies. We are reminded of Einstein's letter to FDR about the potential for an atom bomb. Einstein understood the emerging field of nuclear physics and could see its implications. Einstein himself said: "Imagination is more important than knowledge. For knowledge is limited whereas imagination embraces the entire world, stimulating progress, giving birth to evolution."



"I look through a half-opened door into the future, full of interest, intriguing beyond my power to describe, but with a full understanding that it is for each generation to solve its own problems and that no man has the wisdom to guide or control the next generation."

William J. Mayo, 1931*

* See https://history.mayoclinic.org/toolkit/quotations/the-doctors-mayo/

Building Value: Seize the Opportunity

The most important thing is to spot an innovative idea for a big market and get moving.

- Life in biotech companies can involve years of routine activity and decision-making accompanied by a few moments when a critical decision must be made after an opportunity presents itself:
  - The organization *needs to spot the opportunity and react accordingly.* Preparation is everything.
  - Typically, this involves *good commercial analysis* and an ability to analyze imperfect clinical data and associated MOA analysis.
  - The leader of the organization needs to make the right decision and do so quickly
  - The organization's board needs to support the leader in the decision
  - The business development / finance function can become very critical at such a moment. Needs to *facilitate getting the deal done* rather than *getting in the way*.
- Examples of defining moments in our industry:
  - Pfizer's reaction to the SARS-COV2 pandemic. Defined what was needed and cut a deal rapidly with BioNtech. Then invested in an antiviral. Executed well. Pfizer delivered *twice* during the pandemic. Others delivered *zero*.
  - Horizon Pharma's reaction to the River Vision teprotumumab opportunity. The CEO worked with BD to get the deal done in a short period of time. The dataset at hand was small but convincing.
  - Astellas Pharma reaction to enzalutamide. In the words of an Astellas executive at the time: "The data was there. The need was there, and the deal was there. We did the deal." The dataset was small but convincing.
- Each of the three companies here had undertaken critical preparation to recognize and react to a $20 billion+ value opportunity. Astellas and Horizon both knew that they had made a great decision based on the data seen at the time.

"Luck is when an opportunity comes along and you're prepared for it."

Denzel Washington
(Hollywood Actor)

Source: Getty Images

Quotes on Opportunity and Time

"One part of strategy that many people mistake is that as the time frames get compressed, the ability to quickly react to opportunity becomes a much more important part of strategy."

Reid Hoffman

“I have only two enemies: the disease and the clock.”

Tal Zaks, CMO, Moderna

“If today were the last day of my life, would I want to do what I am about to do today?”

Steve Jobs

Building Value: Learn to Navigate the Unknown

How often do people in business look for one thing and find another thing that is even bigger? And then, miss it?

Framing is an important human trait. Humans all frame what they see, exploring business opportunities with many preconceptions. Humans interpret observations based on those preconceptions. The ability to react appropriately to surprises, what Donald Rumsfeld called “unknown unknowns”, is a critical success trait in drug discovery. The case of Henry Hudson illustrated at right is a classic example of failure to react to new information.

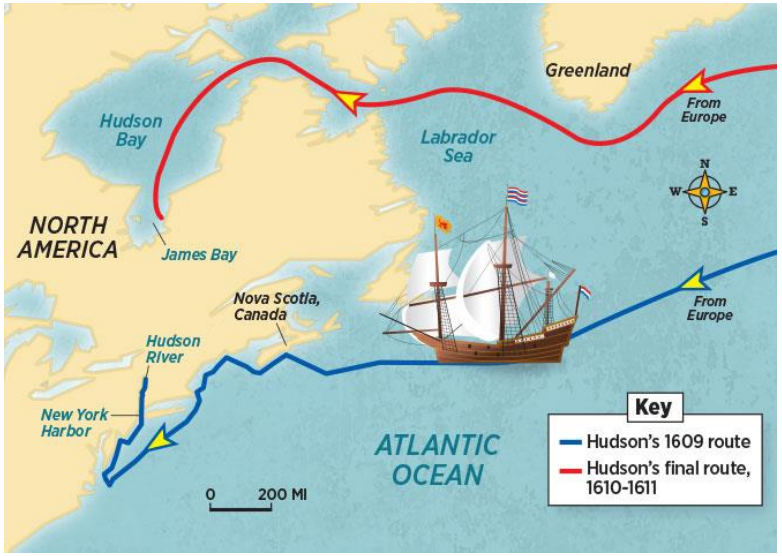
“Perceptive Agility” refers to the ability to recognize an unexpected discovery and react to it appropriately. There are countless examples of serendipitous discoveries in medicine where a scientist had the perceptive agility to recognize the implications of an incidental finding from a trial or experimental result.*

The Case of Henry Hudson

Henry Hudson was an entrepreneur of his day. He went on three voyages searching for the “Northwest Passage” – a short cut from Europe to Cathay.

He never found it, but he did discover New York Harbor, Manhattan and the Hudson River in 1609.

Hudson did not understand the importance of his discovery. The New York area (and Northeast) was *far more* important than the route to Cathay. Hudson died in a mutiny in James Bay not knowing how important his voyages were.

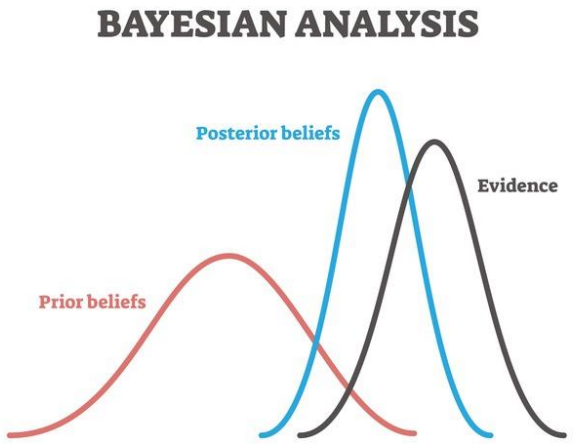


* See, for example: https://www.theguardian.com/lifeandstyle/2017/jul/11/from-viagra-to-valium-the-drugs-that-were-discovered-by-accident

Building Value: Identification of Signal

Doing diligence is all about looking for signal amidst noise while identifying show-stoppers.

- We have discussed the importance of avoiding bias, doing the work and looking for large markets.
- Diligence is about looking for show-stoppers such as toxicology observations and their meaning.
- But how do you spot opportunity amidst noise?
- One might start by saying we should look for clinical trial data that had statistically significant results.
- We would suggest that this is not necessarily the right approach. If the data is so good and the molecule excellent, it probably will not be affordable and a source of value creation.
- Bayes' Theorem says that we should consider prior beliefs when evaluating evidence and we should also update our beliefs based on the underlying probability distribution of an event if a hypothesis were not true.
- To illustrate, FibroGen raised substantial capital in 2004 based on six patients of data for a HIF-2a inhibitor (FG-2216). All six patients had anemia at baseline and all six no longer had anemia after treatment with drug. Because the probability of spontaneous resolution of anemia is close to zero, this meant that the probability that the drug was active was very high even though the results were not statistically significant.
- In both the Astellas / Enzalutamide and Horizon / Tepro examples, the datasets BD teams had to go on at the time were small. But the signals were very strong. Signal extraction from small datasets, single-arm studies, anecdotal data and circumstantial evidence is a critical skill in biotech business development and value creation.



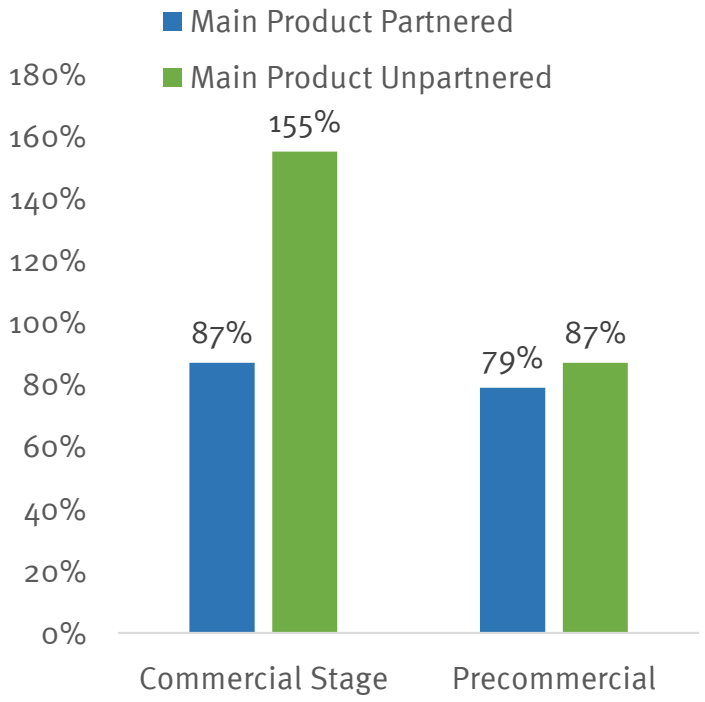
Statistical significance in a clinical trial is much less important than how much we update our beliefs after a clinical trial based on observed data and an understanding of how likely the observed data could have been due to chance.

Building Value: Knowing When Not to Sell or Partner

Many biotech companies exit through M&A fairly quickly or enter into partnership deals. The alternative is to "go alone".

- We have found over the years that investors assign higher valuations to companies that have unencumbered products. See chart at right.
- Most biotech investors would prefer to invest in companies that have unencumbered products.
- The reason is obvious: the company is more likely to capture an M&A premium if its lead product is unencumbered.
- We have found that a valuable tool is to create a value trajectory (see next page). This would show what a company would be worth on an unencumbered basis at each point of development.
- One can then compare the cost and risk to get to each point of development to the value consequences of doing so. For example, suppose it costs $100 million to go from good Phase 2 data to good Phase 3 data but you think there is only a 50% chance of getting there. Otherwise, the data will be a complete miss. Suppose, the value of your company with good Phase 2 data is $300mm but $2 billion with good Phase 3 data. Then, you have a 50/50 shot at gaining $1.7 billion in value and it will cost you $100mm.
- The probabilized payoff is .5 x 1700mm =$850mm versus $100mm investment. This is probably an investment you want to make.
- On the other hand, if the friendly neighboring big pharma wants to pay you $2 billion, you might want to look at that. However, even then, you need to work your way down the full value trajectory to see if this makes sense.

Average Ratio of Enterprise Value (in Stock Market) Divided by NPV Value of Assets (according to analyst consensus), March 2019 (N=22)

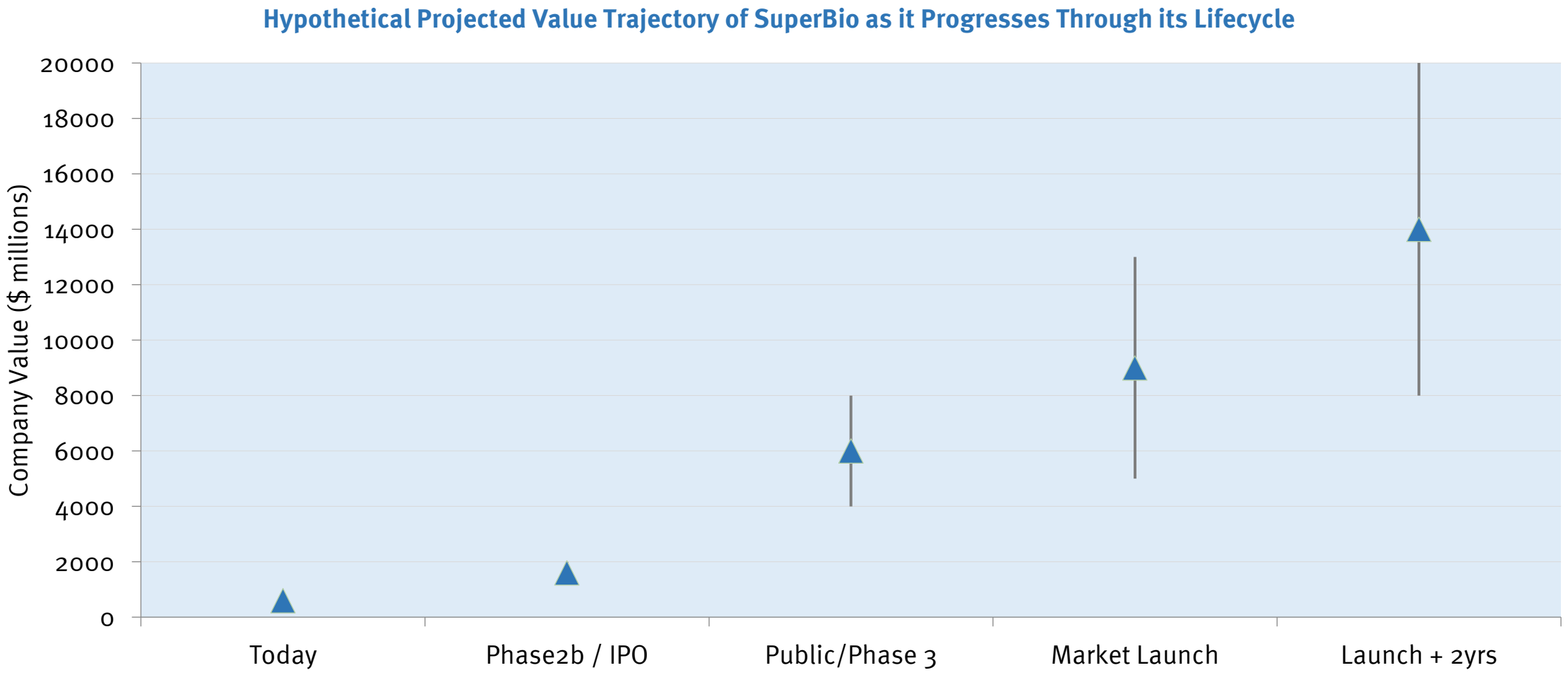


Companies with unpartnered lead products tend to trade at higher valuations, particularly after they reach the commercial stage.

Source; CapitalIQ, Stifel Analysis

Value Trajectory Analysis

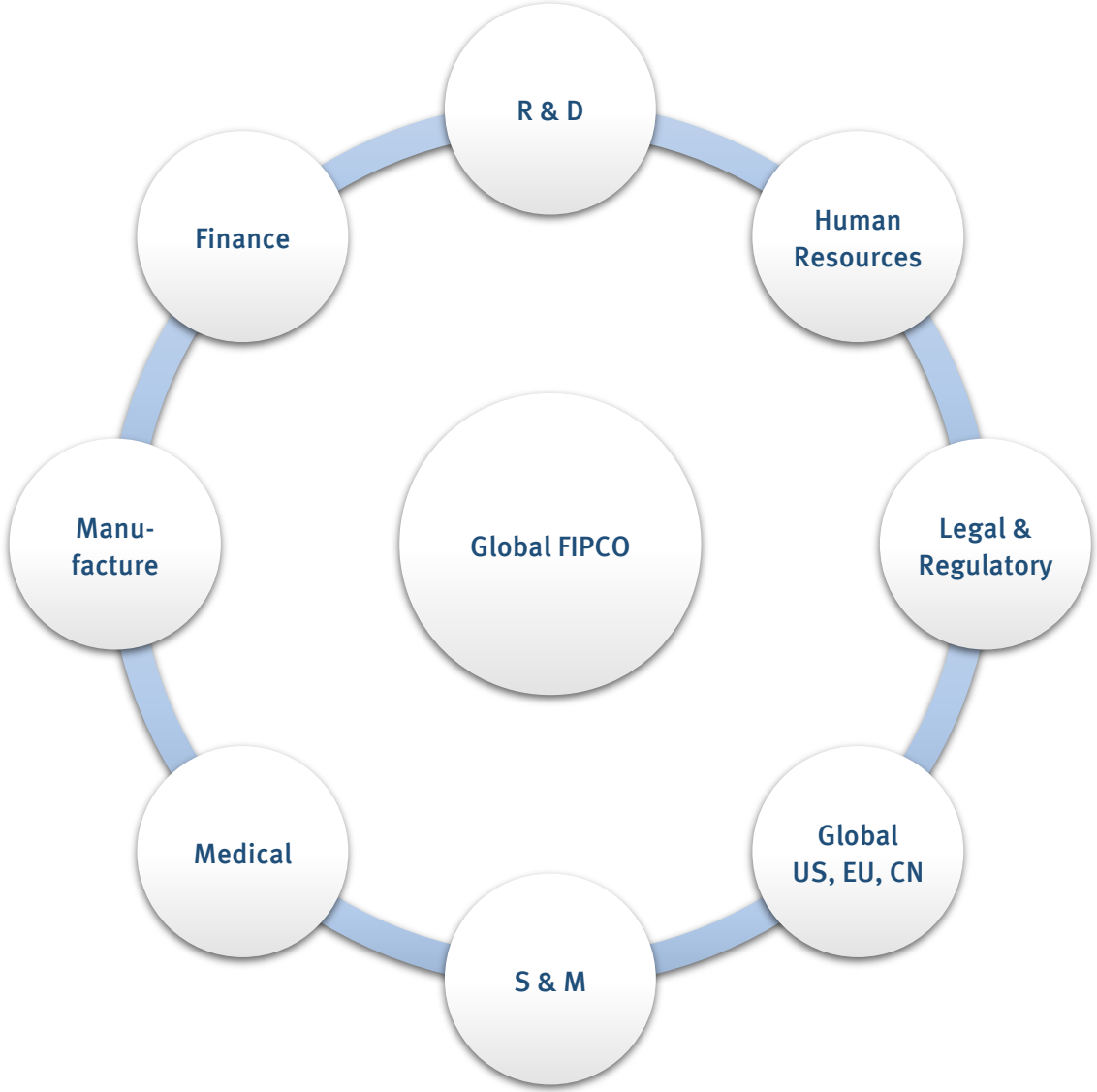
Shows you the expected value and range of values at each point of development of a biotech company.



Building “Go Alone Scenarios”

For a company to transition to the commercial stage, typically involves becoming fully integrated – known as a FIPCO

- We often suggest preserving the option of becoming a large global player for a long as possible.
- Some refer to this as a FIPCO (fully integrated pharmaceutical company) strategy.
- For brevity, we will refer to this as the “Global FIPCO” strategy.
- The cost of this is (1) the biotech company takes the clinical risk on its asset, (2) the biotech will need to dilute current shareholders to preserve the option and (3) a pharma partner may be able to add value in the clinical development and regulatory approval process. This is lost.
- But, the upside may more than justify the cost because investors will pay a premium above and beyond the NPV of cash flows on a partnered product.
- That is, even if a positive NPV partnership for the lead product could be found, investors still might pay more for the biotech stock without the partnership.
- Access to capital will almost certainly not be the constraint in today’s market.
- Partnering rights in some regions (e.g, Japan/China) can make sense if the economics are right.
- The option of partnering a lead product and going back to develop more products would be to be an R&D company (RDCO). Some companies have a comparative advantage in this.



Hypothetical Costing of a "Go Alone Scenario"

In this case a company takes on a very expensive launch of a diabetes products on its own in the U.S. market.

To match Lilly, AZ and Sanofi in diabetes care the biotech would need between 1,200 and 1,400 sales reps plus another 80 medical liaison personnel. This would cost between $600mm and $700mm a year. This presence would be easy to justify with a single blockbuster product in diabetes care. Attracting sales personnel should be relatively easy given that many are selling legacy insulins and DPPIV's which are becoming obsolete. Moreover, the largest sales forces are at companies where potential for appreciation of employee options is low.

Size of U.S. Diabetes Sales Force and Revenue Production Among Top Six Pharmaceutical Companies in the Field, 2018

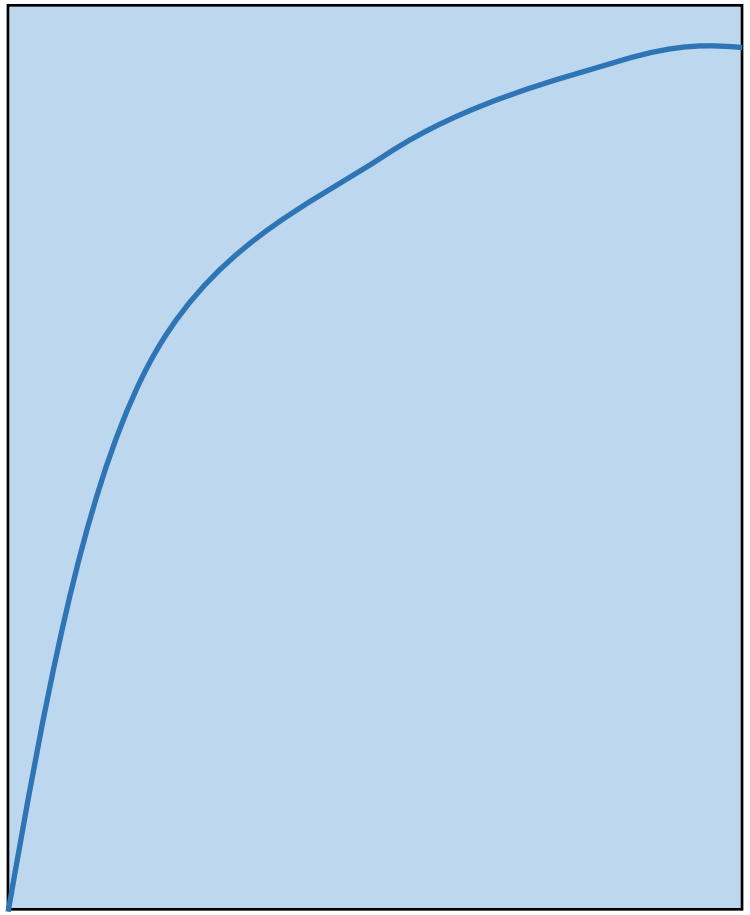
Company	Franchise	Number of Reps	U.S. Diabetes Revenue (2018)	Revenue / Rep	Key Products
Novo Nordisk	Growing	3,448	$7,180,000,000	$2,082,367	Victoza, Ozempic, NovoRapid, Levemir
Eli Lilly	Growing	1,324	$6,464,000,000	$4,882,175	Trulicity, Humalog, Humulin
Boehringer-Ingelheim	Growing	357	$624,000,000	$1,747,899	Jardiance, Trajenta
Sanofi	Declining	827	$2,490,000,000	$3,010,883	Lantus, Toujeo, Apidra
Merck	Declining	384	$2,780,000,000	$7,239,583	Januvia, Janumet
AstraZeneca	Growing	1,684	$1,397,000,000	$829,572	Farxiga, Onglyza, Bydureon
	Average	**1,337**	**3,489,166,667**	**$3,298,747**	

Source: LinkedIn analysis for rep counts (allocated general reps by fraction of U.S. sales in diabetes care). Company annual reports or press releases used to obtain U.S. diabetes revenue.

Hypothetical Comparison of FIPCO to Partnering

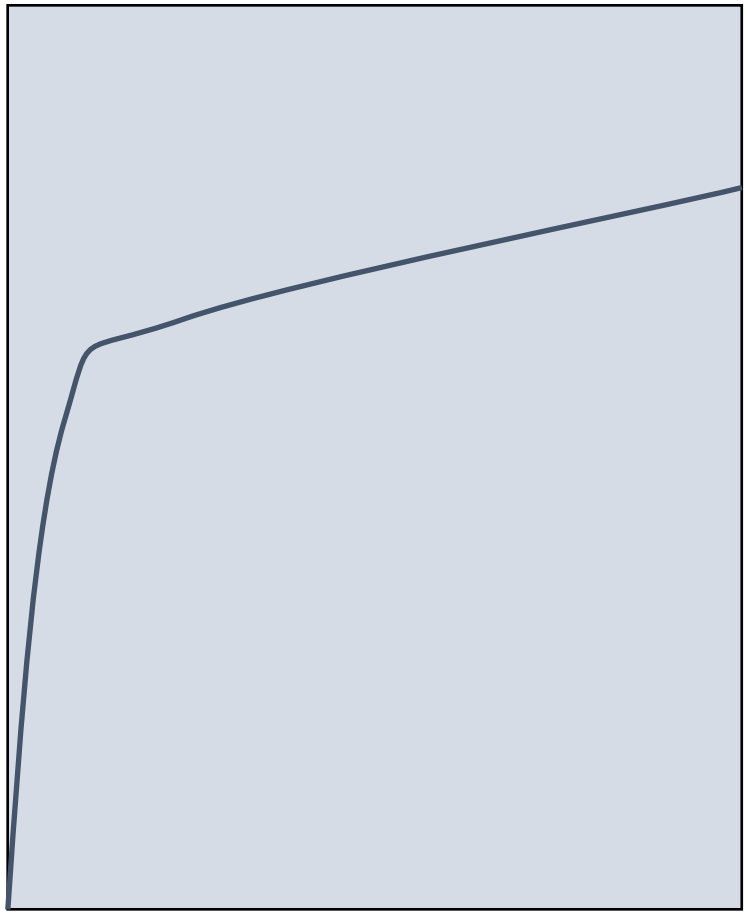
Slower Ascent But Likely to Achieve Lower Long-Term Value

Hypothetical Value Trajectory With Outside Capital (FIPCO)



Faster Ascent But Likely to Achieve Lower Long-Term Value

Hypothetical Value Trajectory With Partnerships on Key Products (RDCO)



Each alternative has different implications for value creation. Raising equity capital means dilution of current equity holders interest in future value. Partnership deals dilute future revenue.

Quotes on M&A Strategy

“You’re either at the table or on the menu”

Al Capone

“You've got to know when to hold 'em
Know when to fold 'em
Know when to walk away
And know when to run”

Kenny Rogers, Country singer and legendary biotech strategist

“I have never cared what something costs; I care what its worth”

Ari Emanuel, Talent Agent

Biotech companies are bought not sold. As Jimmy Buffet says, “If the phone doesn’t ring that will be me.”

Anonymous

“Let us never negotiate out of fear. But let us never fear to negotiate.”

John F. Kennedy

“Don’t wrestle with pigs. You both get dirty and the pig likes it.”

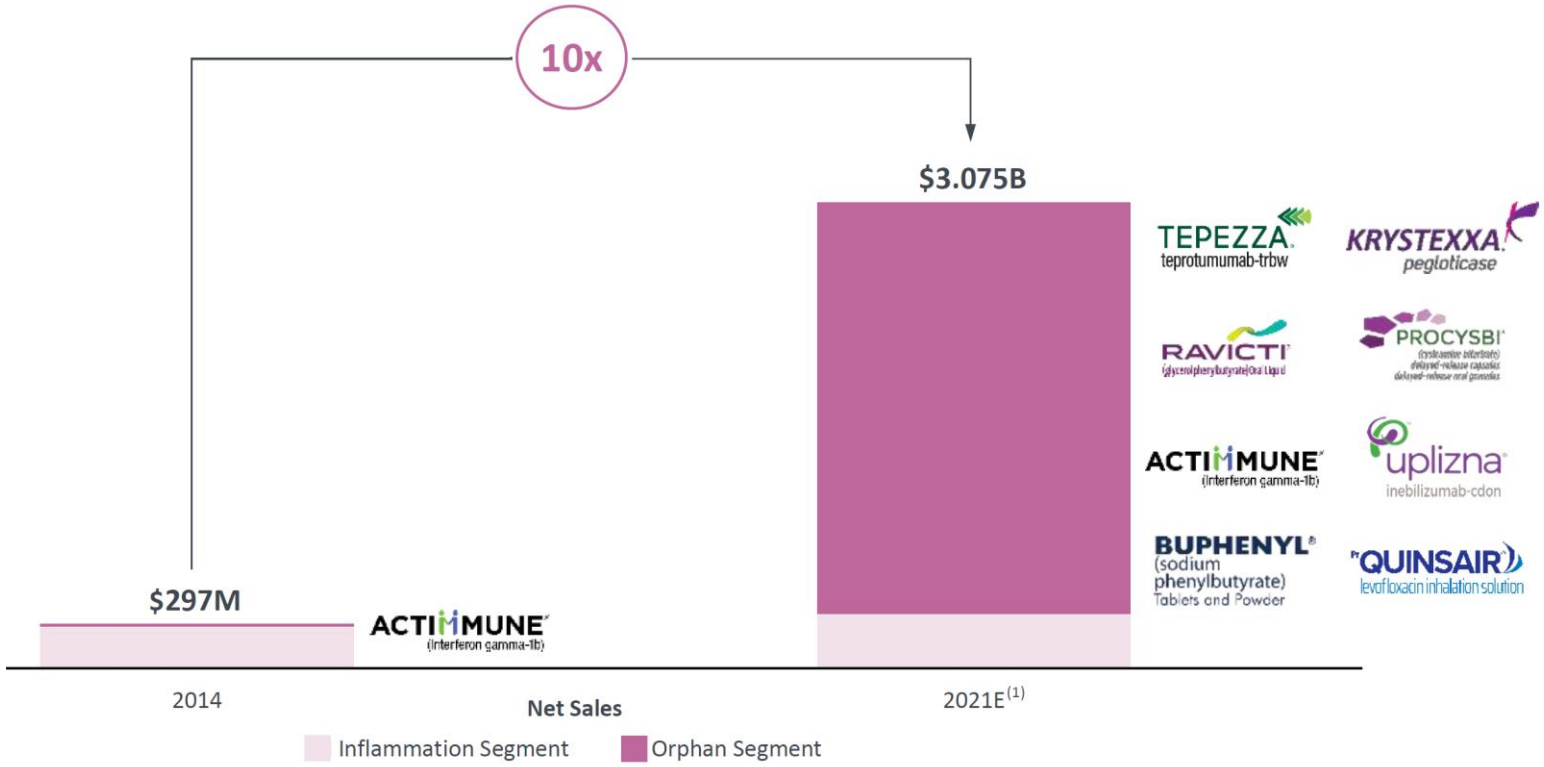
Mark Twain

“Americans make money by playing money games, namely mergers, acquisitions, by simply moving money back and forth … instead of creating and producing goods with some actual value.”

Akio Morita, Sony

Horizon's Transformation

Horizon increased sales by 10x by buying late stage or commercial assets with high market potential.

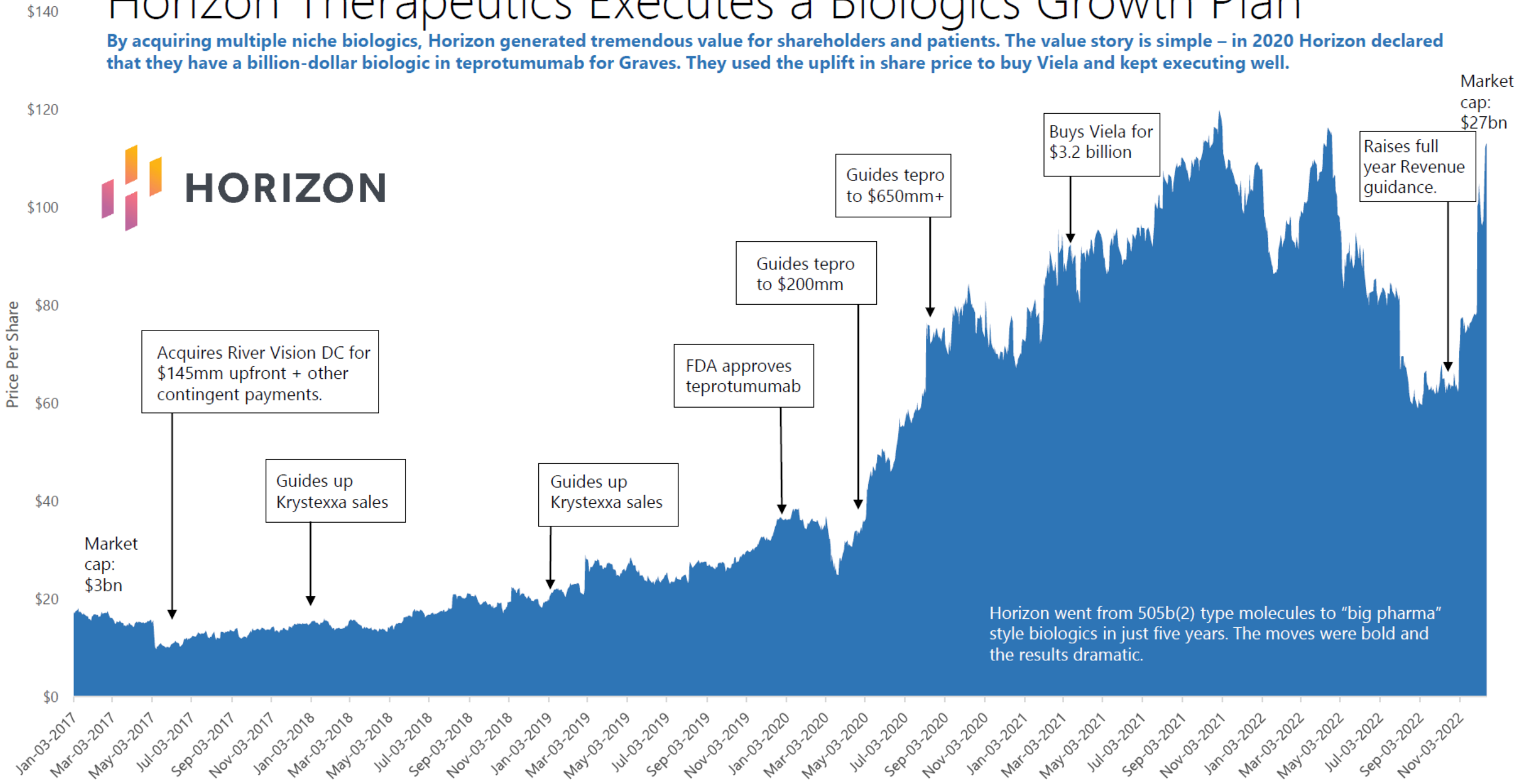


- Company built up a strong R&D function and unparalleled business development and commercial analytics team.
- Spent first three years building up an organization.
- Had broad search parameters (rare and inflammation) and was ready to strike when the two key deals arrive (teprotumumab in 2017 and Krystexxa in 2015).

Slide from Sep 2021, Horizon Therapeutics R&D Day.

Horizon Therapeutics Executes a Biologics Growth Plan

By acquiring multiple niche biologics, Horizon generated tremendous value for shareholders and patients. The value story is simple – in 2020 Horizon declared that they have a billion-dollar biologic in teprotumumab for Graves. They used the uplift in share price to buy Viela and kept executing well.



Source; CapitalIQ, Stifel Analysis

Summary of Key Points of Biotech Value Creation

Principle	Comment / Case Study
Large Products are Key.	The recent history of the pharma industry shows that value creation accrues disproportionately to companies with large products.
Avoid biases. Be flexible.	The most important thing is to spot a big opportunity for a big market that others somehow miss. Merck pivoted rapidly to Keytruda®, a drug they had previously ignored and went all in on the bet.
Be decisive and smart.	One can compete against giants using brains and time rather than brawn as weapons. Run killer experiments. Aim for high efficacy. Look where others don't. And be decisive when others hesitate. A great example is how Pfizer reacted rapidly and decisively to the COVID-19 pandemic despite their large, sprawling organization.

The Movie “Moneyball” and Biotech

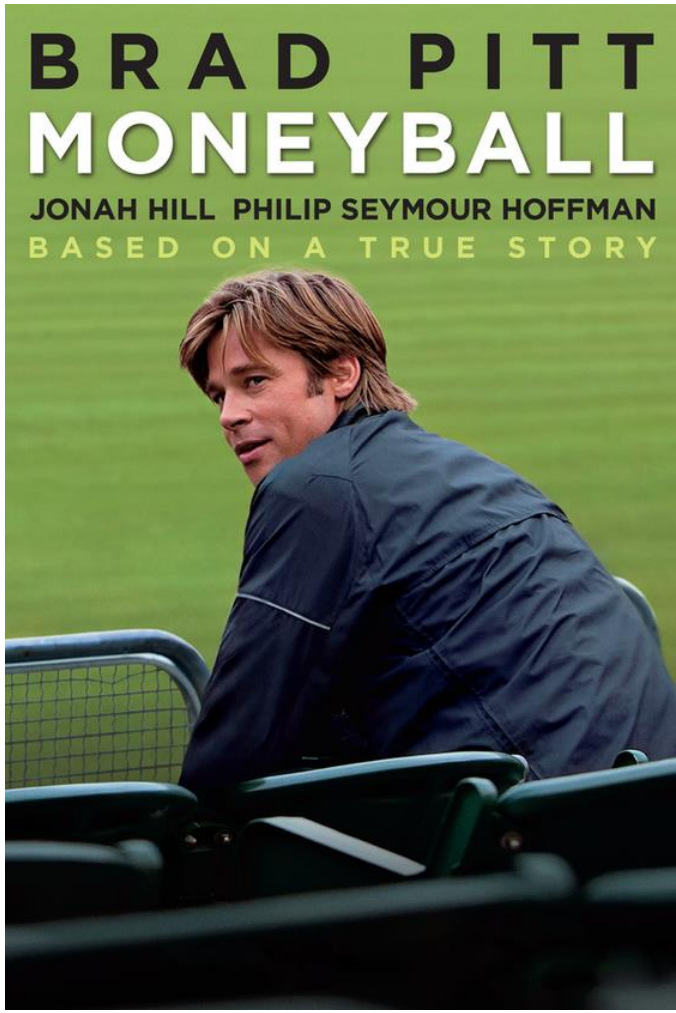
The book and movie “Moneyball” talks about traditional scouting for baseball players versus a quant model for what players could be worth.

The approach is constrained insofar as one needs to find the highest value player for each position (e.g., pitcher or outfielder).

The story in the book is that the model beats the scouts easily and the Oakland “A’s” post a 20-game winning streak and dramatically improve performance.

Today, most of the baseball field combines quantitative scoring of players with scouting for the players but no one lets their scouts do all the thinking anymore.

We can quantify value on the market using statistical models of what investors value in biotech. But, we still need to use scouting methods to find good assets to fill the evaluation funnel.



Back to Finance and Valuation in Business Deals: Moneyball and Arbitrage in Biotech

It's good to look for arbitrage situations when considering asset acquisitions

- Measure value of assets using a "Moneyball" model
- This model maps company characteristics to what the market is looking for
- Can be thought of as a highly sophisticated comparables model and spits out a specific value for a company

There are two ways in which money is made in biotech:

- **Cash and carry arbitrage.** Find an asset that is worth much more today on the public market than one pays for it. A great example is the Endocyte / ABX deal. These are rare but possible.
- **Risk arbitrage.** Find an asset that is one step away from being worth a significant amount on the public market. The typical inflection point would be a clinical study. The expected probabilized "Moneyball value" of the asset is significantly more than one is paying for it.

Biotech Market Mapping to Build Moneyball Models

- Take the universe of public therapeutics companies in a specific area – e.g., virology.
- Rate the companies along individual characteristics such as quality of their efficacy data, how good are their patents, time to market etc.
- Create a least squares regression model that maps enterprise value to the variables you have measured.
- Take candidate acquisition candidate “A”.
- Suppose, it would cost $30 million to buy.
- The regression model spits out that it would be worth $120mm today.
- We call this “Moneyball Value”.
- Value creation would be $90mm.
- There is a more technical term for this type of model. Professional economists call these models “hedonic pricing models” as they associated characteristics with value (hedonic value).*
- The website Zillow will tell you the value of a house (in the U.S.) and does so using a sophisticated multivariate hedonic pricing model for housing similar to that we use for biotech.**

* See Sherwin Rosen, “Hedonic Prices and Implicit Markets: Product Differentiation in Pure Competition,” *Journal of Political Economy*, Vol. 82, No. 1 (Jan. - Feb., 1974), pp. 34-55
** See https://www.mdpi.com/2073-445X/11/3/334

“Moneyball” Study of Public Oncology Company Valuations

We looked at the universe of publically-traded oncology therapeutics companies in April 2020

- We derived a list of publically-traded oncology therapeutic companies from a search of all publicly held biotech companies worldwide that was extracted from CapitalIQ in January 2020.
- We looked at each company and noted whether or not it’s main area of focus was oncology therapeutics. Companies were identified by searching for the words “cancer”, “tumor” and “oncology” in business descriptions.
- In total, we identified 255 publically traded oncology companies. To focus on pure play oncology, we excluded companies whose lead asset was not an oncology asset. We also left out large Pharmas such as Bristol-Myers Squibb, Merck or Roche who are oncology focused. There were 242 remaining companies in our dataset after removing companies (like Xencor) who’s lead asset is not in oncology.
- We collected data on each company including market cap, cash and enterprise value from S&P CapitalIQ. We also collected information on headquarters location, the therapeutic subarea of the company’s lead drug candidate, the MOA area and the phase of development of the lead compound by reviewing each company’s press releases, web site and corporate presentation. We also looked at whether there was any efficacy data and whether the most relevant efficacy data was single arm or double arm.*
- Its important to note that the valuations were obtained well after the NASDAQ Biotech market dropped significantly in the wake of the spread of the COVID-19 virus.
- We also collected several more subjective variables:
  - Quality of the efficacy data on the lead compound. We looked at evidence of survival benefit, the number of CR’s, PRs and SD’s relative to the sample size and what others have seen in similar stage tumors.
  - Size of the market. If a company is focused on third line PTCL that would be classified as a small market. If a company is focused on TNBC or NSCLC with a second- or third-line therapy that would be classified as a large market. If a company is targeting second line ovarian cancer, we would classify this as a medium-sized market.

* We defined thirteen therapeutic sub-areas including six in immuno-oncology. We split the field of targeted therapies into targeted oncology (catch all for mAbs / small molecules going after a specific kinase or related target), precision oncology (molecules aimed at correction oncogenic mutations or hitting very difficult-to-drug targets), ADCs (molecules that deliver a “bomb” to cancer cells by attaching it to an antibody or other binder that preferentially targets cancerous cells) and oncology metabolism (drugs that try to shut down the ability of a tumor to access or consume energy). Many companies operate in multiple sub-areas. In general, we looked at the company’s lead drug candidate to determine its subarea.

Companies Looked at in the Study

These companies are from 23 countries and had a collective market cap of a quarter trillion dollars. Their median enterprise value was $76mm and median cash balance was $42 million (as of April 2020).

4SC
AB Science S.A.
Abion
ABL Bio
Acacia Pharma
Actinium Pharmaceuticals
Active Biotech
Adaptimmune Therapeutics
Aduro BioTech
Advaxis, Inc.
Affimed
Agenus
Agios
Aileron Therapeutics
AIM ImmunoTech Inc.
Alligator Bioscience AB
Allogene Therapeutics
Alphamab Oncology
Alpine Immune Sciences
Amplia Therapeutics
Anchiano Therapeutics
Anixa
Aprea Therapeutics
Aptose Biosciences Inc.
Aravive
Arcus Biosciences
Arvinas
Ascelia Pharma
Ascentage Pharma
Atara Bio
Athenex, Inc.
Atreca, Inc.
Autolus
BeiGene
Bellicum Pharmaceuticals
BerGenBio ASA
Betta Pharma
BeyondSpring Inc.
Bicycle Therapeutics
Bioasis Technologies
Bioinvent International
BiolineRx
BioNTech SE
Bio-Path
Black Diamond Therapeutics
Blueprint Medicines
BriaCell Therapeutics
Brightpath BioTherapeutics
Calithera Biosciences
CanBas, Co.
Cantargia
Celldex
Cellectis
Cellid, Inc.
Cellular Biomedicine
CEL-SCI Corporation
Celsion
Checkpoint Therapeutics
Chimerix
Cleveland BioLabs
Clovis Oncology
CNS Pharmaceuticals
Compugen
Constellation Pharmaceuticals
Corvus Pharma
Cotinga Pharmaceuticals
Cstone Pharma
CTI Biopharma
Cue Biopharma
Curis, Inc.
Cyclacel Pharmaceuticals
CytomX Therapeutics
CytRx Corporation
Deciphera Pharmaceuticals
DelMar Pharmaceuticals
Dextech Medical AB
Eagle Pharmaceuticals, Inc.
Enlivex Therapeutics
Epizyme
ERYTECH Pharma
ESSA Pharma
e-Therapeutics
Eutilex
Exelixis
Faron Pharmaceuticals
Fate Therapeutics
Fennec Pharmaceuticals Inc.
Five Prime
G1 Therapeutics
Galera Therapeutics
Gamida Cell
Genmab A/S
Genocea
Genprex
Geron Corporation
Glycomimetics
Glyconex
Gritstone Oncology, Inc.
GT Biopharma, Inc.
Hamlet Pharma AB
Harpoon Therapeutics
Heat Biologics
Heidelberg Pharma
Helix Biopharma
Hengrui Medicine
Heron Therapeutics
Humanigen
Hutchison China Meditech
IDEAYA Biosciences
Idera Pharma
IGM Bio
I-Mab
Immunicum
Immunogen
Immunomedics
Immutep
Imugene
IMV
Incyte
Infinity Pharmaceuticals
Inhibitor Therapeutics, Inc.
Innate Pharma
Immunicum
Immunogen
Immunomedics
Immutep
Imugene
IMV
Incyte
Infinity Pharmaceuticals
Inhibitor Therapeutics, Inc.
Innate Pharma
InnoCare Pharma
Innovent
Inovio Pharmaceuticals
Invion Limited
Iovance Biotherapeutics
Isofol Medical
Isoray
Jazz Pharma
Jounce Therapeutics
Karyopharm Therapeutics
Kazia Biopharma
Kiadis Pharma
Kura Oncology
Leap Therapeutics
LIDDS AB
Lixte Biotechnology
Macrogenics
Magenta Therapeutics
Marker Therapeutics
Medicenna Therapeutics
Medigen Biotechnology
Medigene AG
Medivir
MedPacto
MEI Pharma
Mersana Therapeutics
Merus
Mirati Therapeutics
Molecular Partners AG
Molecular Templates
Moleculin Biotech
Monopar Therapeutics
Morphosys
Mustang Bio, Inc.
Nanobiotix
Nantkwest
Nascent Biotech, Inc.
Nektar Therapeutics
Neoleukin Therapeutics
Nextcure
Nordic Nanovector
Northwest Biotherapeutics
Noxopharm
NOXXON Pharma N.V.
Nucana
Nuformix
Oasmia Pharmaceutical AB
OBI Pharma
Odonate Therapeutics
OncBioMune Pharma
Oncology Pharma Inc.
Oncology Venture A/S
Oncolys BioPharma
Oncolytics Biotech
Onconova Therapetuics
Oncopeptides AB
OncoSec Medical Incorporated
Oncotelic
OncoTherapy Science
Oncternal Therapeutics
Ono Pharma
Onxeo
OSE Immunotherapeutics
Patrys Limited
PCI Biotech
PDS Biotech
PharmaCyte Biotech, Inc.
PharmaMar SA
Pieris
PledPharma AB
Plus Therapeutics, Inc.
Precision BioSciences
Prescient Therapeutics
Progenics Pharmaceuticals
Provectus Biopharmaceuticals
Puma Biotechnology
Q Biomed
Race Oncology
RAPT Therapeutics
Redx Pharma
Replimune Group, Inc.
Revolution Medicines
Rexahn Pharmaceuticals
RhoVac
Rubius Therapeutics
Ryvu Therapeutics
Salarius Pharmaceuticals
Scancell Holdings plc
Seattle Genetics
SELLAS Life Sciences
Senwha
Sesen Bio, Inc.
Sierra Oncology
Silliajen
Soligenix
Sorrento Therapeutics
Spectrum Pharmaceuticals
Spring Bank Pharmaceuticals
SpringWorks Therapeutics
Stemline Therapeutics
Sun Biopharma
Sunesis Pharmaceuticals
Surface Oncology
Sutro Biopharma
Syndax Pharma
Syros Pharmaceuticals
Targovax
TCR2
Telix Pharmaceuticals
TG Therapeutics
TOT Biopharm
TRACON Pharma
Transgene
Trillium Therapeutics
Trovagene
Turning Point Therapeutics
Tyme Technologies
Ultimovacs ASA
Unum Therapeutics
Urogen Pharma
Vaccibody
Vaccinex, Inc.
ValiRx plc
Vaxil Bio Ltd.
Vectorite Biomedical
Verastem
Veru
WntResearch
Xencor, Inc.
Y-mAbs Therapeutics
Zai Lab
ZIOPHARM Oncology
Zymeworks

Source: S&P CapitalIQ

A Moneyball Model: Oncology Biotech Stocks in April 2020

63% of the variability in the enterprise value of public oncology companies can be explained by seven variables.

Dependent variable: Log of enterprise value

Independent variables:

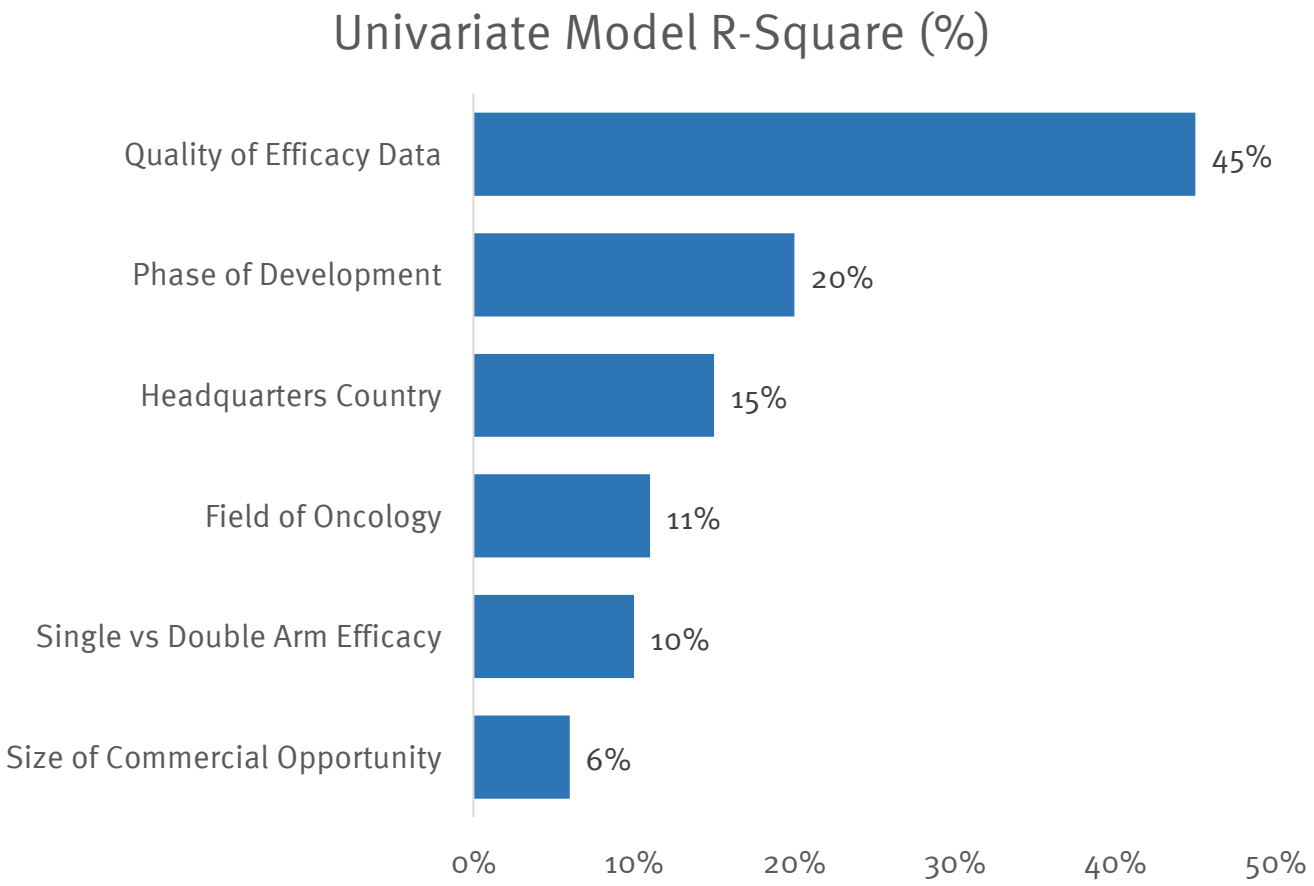
Size of the commercial opportunity
Headquarters country
Strength of efficacy data
Phase of development
Solid or liquid tumor target
Area of oncology (e.g., IO Biologics)
Single arm or double arm efficacy

Multivariate Results:

R-square: 0.63

Source; CapitalIQ, Stifel Analysis

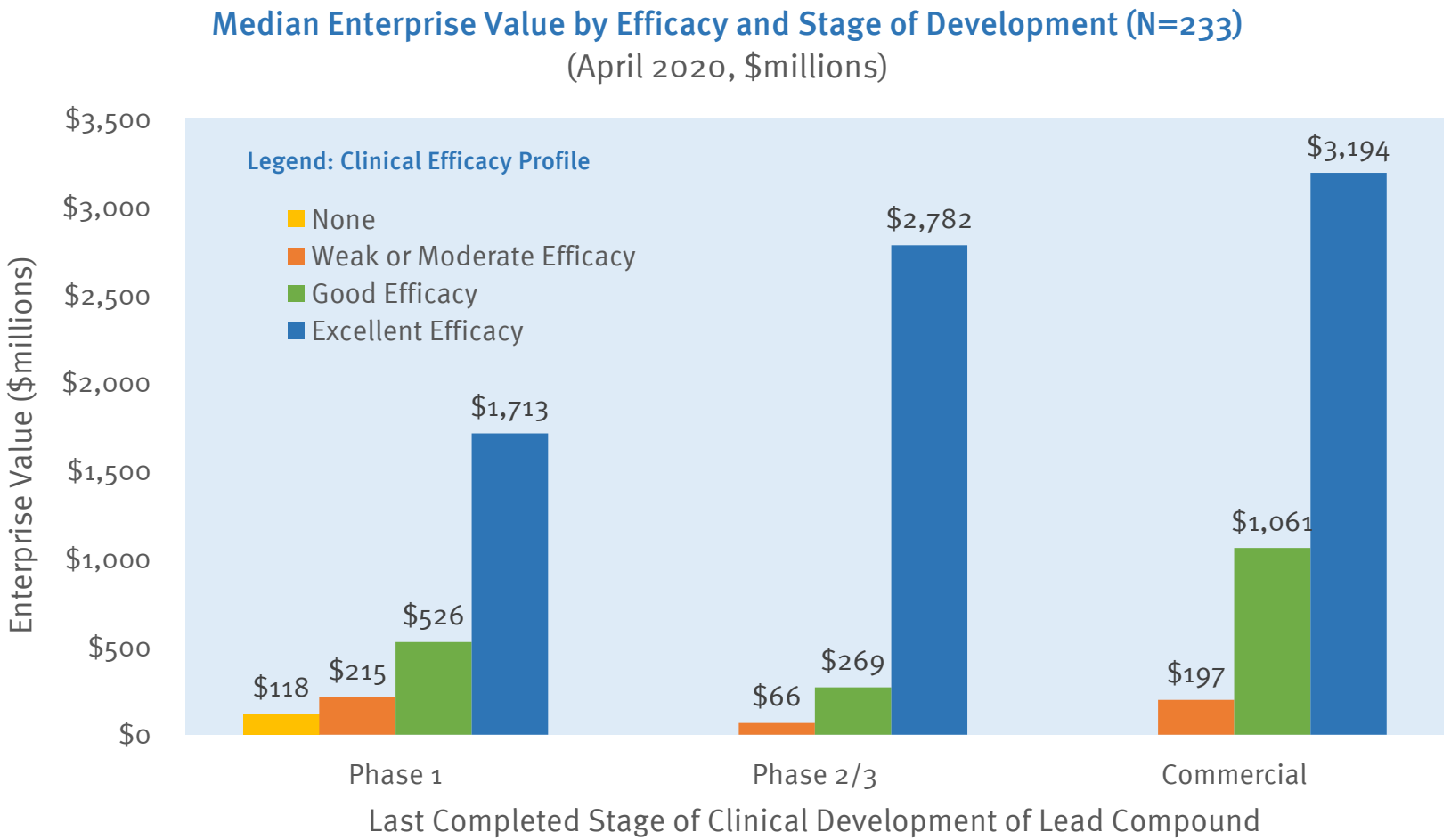
Explaining Value Differentials in Oncology Companies



After weeks of data collection and number crunching, we were surprised to find that a single factor overwhelmingly explained biotech valuations in oncology biotech in 2020: quality of clinical data from an efficacy perspective. Efficacy, it turns out, trumps almost everything else.

Source; CapitalIQ, Stifel Analysis

Drivers of Oncology Biotech Stock Value in April 2020



1. An approval with moderate to weak efficacy data does not contribute nearly as much to value as delivering a product with high efficacy in a Phase 1 study.
2. The most highly valued firms are those with an approval and excellent data.
3. The public markets operate on a "winner take all" basis. The coin of the realm is quality of clinical data.

Source; CapitalIQ, Stifel Analysis

We Did a Similar Exercise in May 2020 for Rare Disease Biotechs

We studied 102 rare disease firms from 14 countries that had a total enterprise value of over $370 billion as of May 15, 2020.

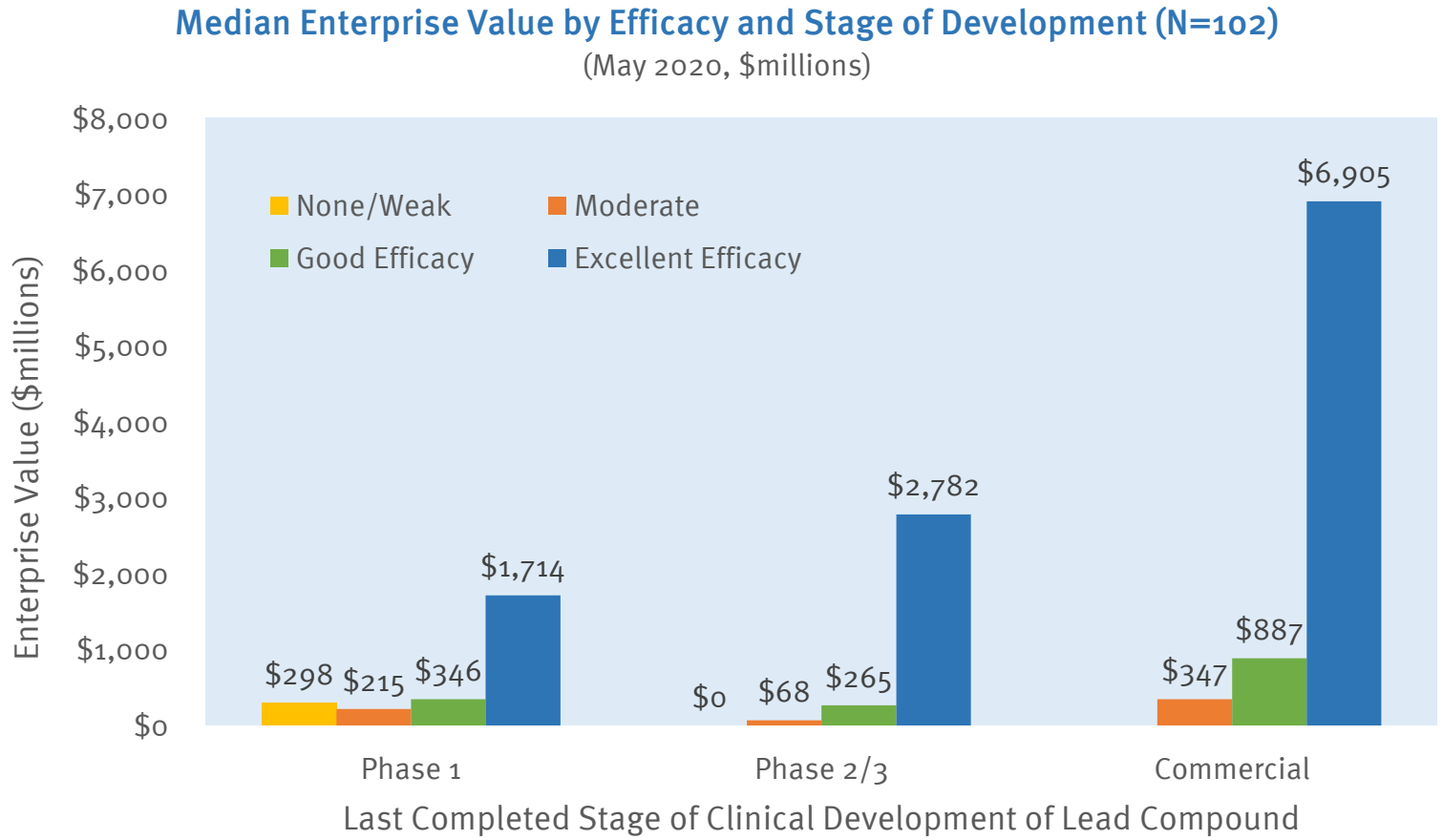
Just like in the oncology study, we carefully collected data on each of these company's lead asset including patent life, quality of dataset etc.

We obtained a model R-square of 0.74 using five variables predicting log EV: Strength of efficacy data (subjective rating), Phase of development, Estimated peak sales (logarithmic), Strength of platform (subjective rating), Length of Exclusivity Period.

Source: CapitalIQ

In Rare Disease Therapeutics We Found that Efficacy is the Main Value Driver Followed by Progress to Approval

An approval with moderate to weak efficacy data does not contribute nearly as much to value as delivering a product with high efficacy after Phase 1 studies. The most highly valued firms are those with an approval and excellent data. The public markets operate on a "winner takes all" basis.



We were struck by the similarity of the findings in rare disease as in oncology.

The "quality premium" – the relative value of an excellent efficacy dataset over a good one was even higher in rare disease therapeutics.

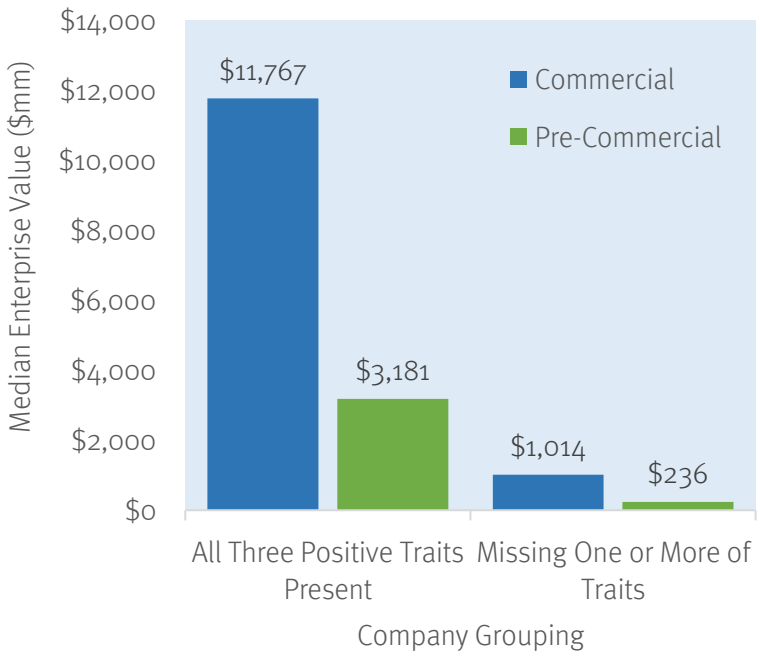
Source: CapitalIQ and Stifel analysis

The “Holy Trinity” in Rare Disease

- We found that an ideal company in the rare disease field would have three positive traits:
  - **Excellent efficacy**: company’s lead drug needs to cure a disease or at least make a major difference in the majority of patient’s that are treated by it.
  - **Long-term exclusivity**: company’s lead drug needs to be protected for the long-run from genericization or reformulation. Seven years of orphan exclusivity does not cut it. To be a “Holy Trinity” company the lead product has to have at least ten years of exclusivity.
  - **Orphan but not ultrarare**: a drug may work great and have excellent efficacy but address so few patients as to not be economically meaningful to investors. We arbitrarily chose a cutoff of 1,000 addressable patients in the US and Europe. Companies whose lead drug addresses fewer than 1,000 patients were excluded from the “Holy Trinity” classification.
- Of the 102 companies in our sample of rare disease companies, 23 were classified as fitting the “Holy Trinity” criteria.
- We mean no disrespect to those who are religious but rather wish to connote the perspective of some industry participants that it is the combination rather than any one trait that really matters in driving value.

We have already noted that companies with better efficacy data trade at higher valuations than others. Here, 23 of 102 companies (23%) check the three key boxes described but they garner 82% of all value of the companies included the dataset. By comparison, we classify 38 of 102 companies as having excellent efficacy data (38%). These companies account for 92% of the value. In general, a rare disease company needs to demonstrate efficacy, market opportunity and long-term exclusivity to garner an outstanding valuation.

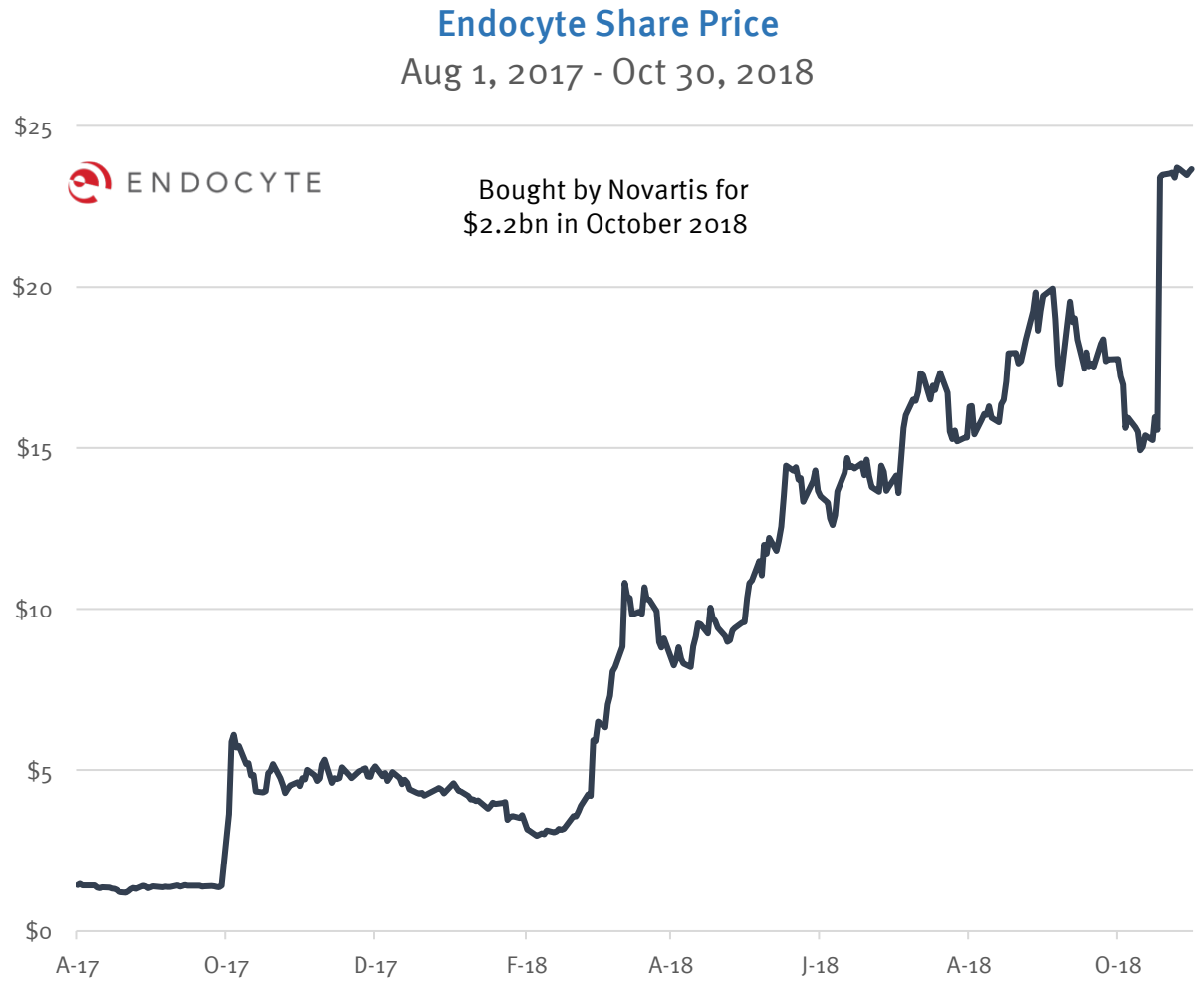
Median EV ($mm) of Companies by “Holy Trinity” Status and Commercialization Status, May 2020 (N=102)



Source: CapitalIQ and Stifel analysis

Case Study: Endocyte "Rebirth" After Issues with Core Folate Targeted EDC Molecules

- Endocyte went through three consecutive clinical failures in the 2014 to 2017 time period.
- Its share price was trading well below cash by mid-2017.
- The organization went through a structured process of searching for additional assets with which to use its excellent organization.
- On October 2, 2017, Endocyte announced that it had in-licensed PSMA-617 from ABX GmbH. It indicated that "Endocyte intends to move quickly into Phase 3 development of 177Lu-PSMA-617, a radioligand therapeutic (RLT) that targets the prostate-specific membrane antigen (PSMA), present in approximately 80% of patients with metastatic castration-resistant prostate cancer (mCRPC)… Lu-PSMA-617 has consistently demonstrated a PSA response (defined as greater than 50% decline from baseline) in 40% to 60% of patients, and a RECIST response rate in soft tissue disease of between 40% and 50%."
- In Feb 2018, Endocyte further announced: ""Following a successful End of Phase 2 meeting with the FDA, we are excited to launch the VISION trial, a phase 3 registration trial of 177Lu-PSMA-617 in patients with prostate cancer".
- Endocyte shares rose 1200% from prior to the licensing deal.



Source: CapitalIQ and Stifel analysis

How Our Model Would Value Endocyte at the Time of ABX Deal

Inputs:
Size of the commercial opportunity: Large
Headquarters country: US
Strength of efficacy data: Excellent
Phase of development: Phase 2
Solid or liquid tumor target: Solid
Area of oncology (e.g., IO Biologics): Radio Pharma
Single arm or double arm efficacy: Single Arm

This is a rare example of a cash-and-carry arbitrage trade in biotech. Endocyte bought an asset for cents on the dollar of what it was worth on the Nasdaq.

Our model values this company as worth **$880 million**
It traded that much by five months after the ABX acquisition even though it paid a very small fraction of that for ABX.
Our model values Endocyte were its lead asset approved at **$3.1 billion**. In a sense, Novartis paid this value with some time discounting since the company had almost fully derisked the asset at the point of approval.

Source: Stifel analysis

Disclosure

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