# Biopharmaceutical Sector

## Weekly Update – October 9, 2023



STIFEL | Healthcare

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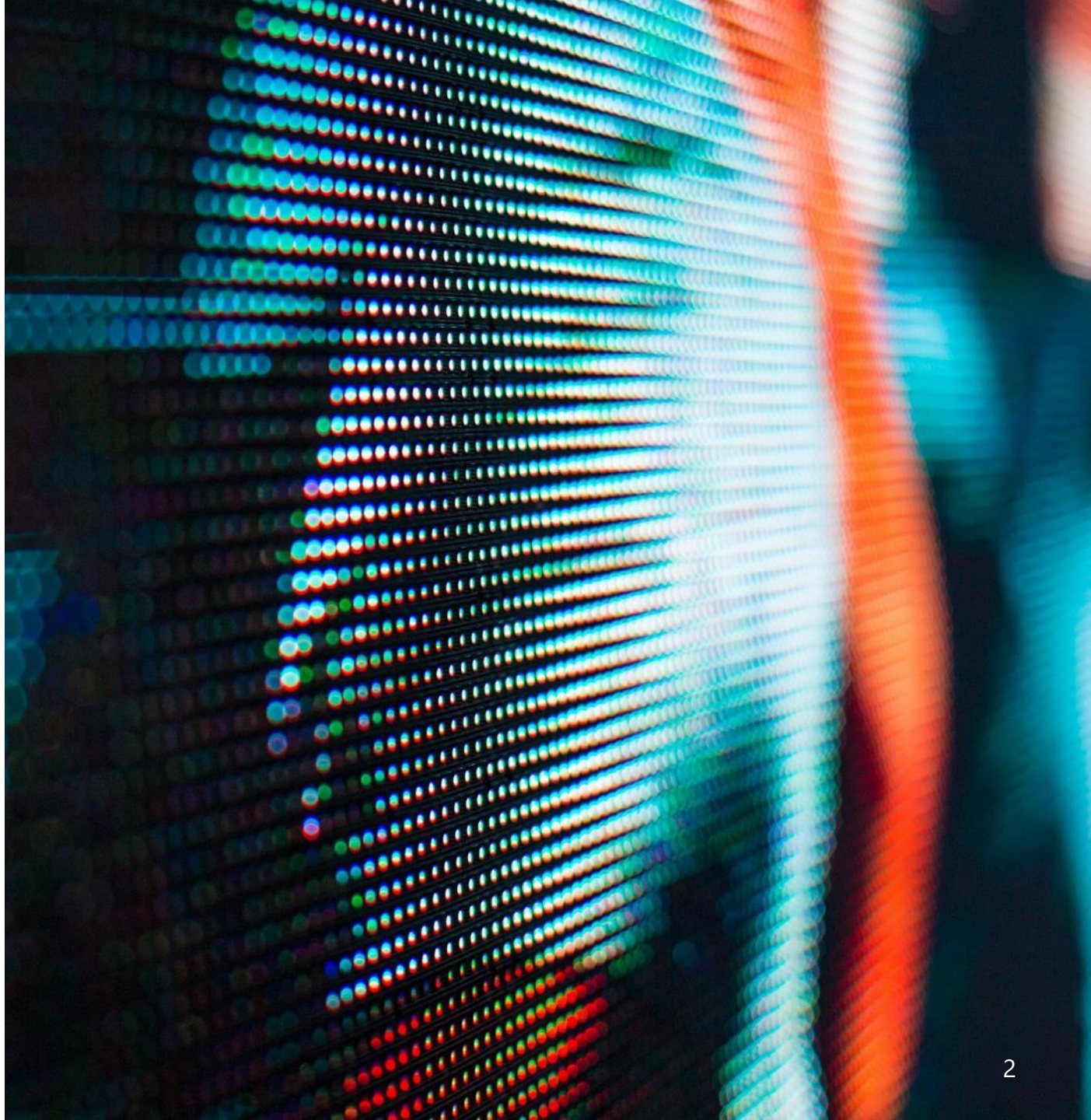

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# Past Issues / Mailing List

If you are not on the mailing list for this publication and wish to be added, please notify Natasha Yeung (yeungn@stifel.com).

Recent issues in case you missed and want to read:

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

Biotech Building Lobby, Mission Bay, San Francisco, CA

# Join Us at These Upcoming Events


Biotech Hangout held its latest event on October 6th.

The next event will be on October 13, 2023.

Please join us.

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

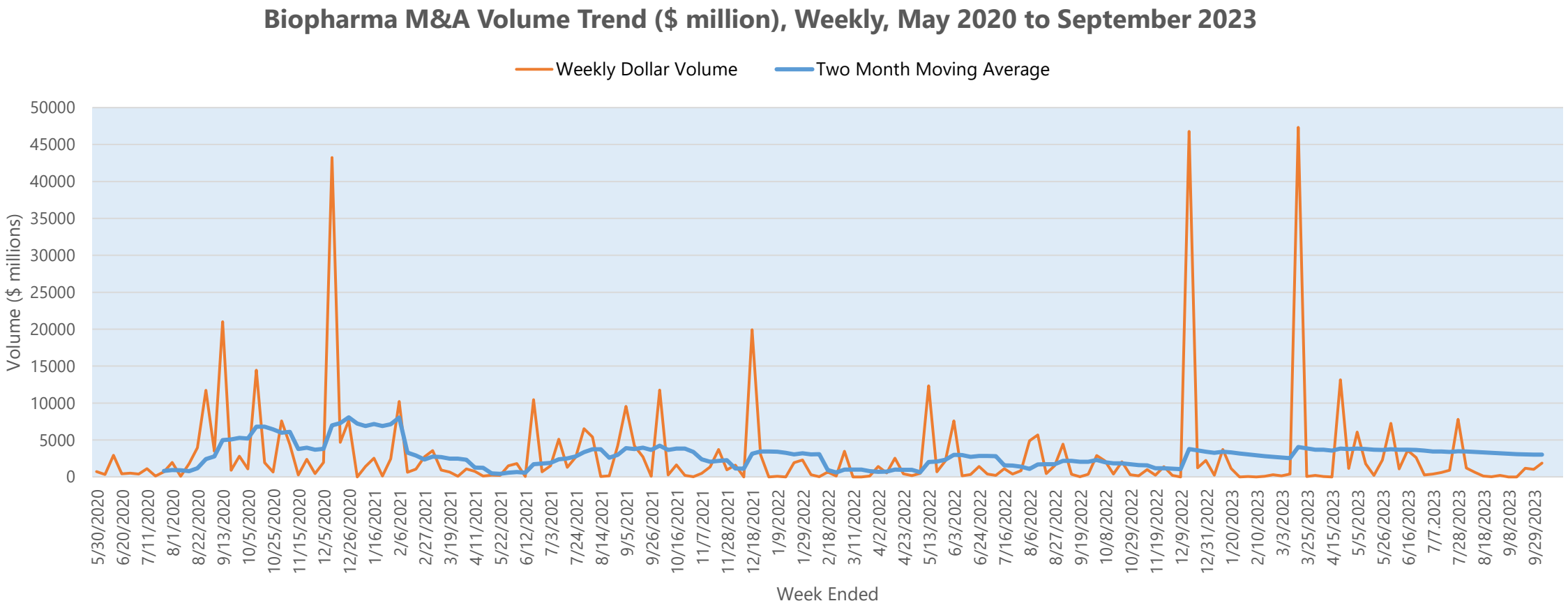

BIO-Europe convenes over 5,500 attendees, representing 60 countries and 2,220+ companies, making the event the industry's largest gathering of biopharma professionals in Europe.

**To Learn More**
https://informaconnect.com/bioeurope/

# Biopharma Deals Environment

# Last Week Saw $6.7 Billion in Announced M&A Volume and $3.2 Billion in Asset Sale Announcements: A $10bn Week

**Last week saw four M&A deals announce: (1) BMS buy of Mirati for $4.8bn plus contingencies, (2) Eli Lilly announced an acquisition of Point Biopharma for $1.4 billion; (3) Kyowa Kirin is acquiring Orchard Therapeutics for $387 million upfront and (4) AbbVie is acquiring Mitokinin for $110 million. In addition, Viatris announced $3.2 billion of asset sales. The Amgen/Horizon deal closed and rumors surfaced of a potential acquisition of Mirati by Sanofi.**




Source: S&P, CapitalIQ

# Bristol Myers Squibb Strengthens and Diversifies Oncology Portfolio With Acquisition of Mirati Therapeutics

**October 8, 2023 PRINCETON, N.J. & SAN DIEGO--(BUSINESS WIRE)**-- Bristol Myers Squibb (NYSE: BMY) and Mirati Therapeutics, Inc.® (NASDAQ: MRTX) today announced that they have entered into a definitive merger agreement under which Bristol Myers Squibb has agreed to acquire Mirati for $58.00 per share in cash, for a total equity value of $4.8 billion. Mirati stockholders will also receive one non-tradeable Contingent Value Right (CVR) for each Mirati share held, potentially worth $12.00 per share in cash, representing an additional $1.0 billion of value opportunity. The transaction was unanimously approved by both the Bristol Myers Squibb and the Mirati Boards of Directors.

Mirati is a commercial stage targeted oncology company whose mission is to discover, design and deliver breakthrough therapies to transform the lives of patients with cancer and their loved ones. Mirati's assets are a strong fit with Bristol Myers Squibb's portfolio and innovative pipeline and represent an attractive opportunity to grow Bristol Myers Squibb's oncology franchise. Through this acquisition, Bristol Myers Squibb will add KRAZATI, an important lung cancer medicine, to its commercial portfolio. The company gains access to several promising clinical assets that complement its oncology pipeline and are strong candidates for single agent development and combination strategies.

"We are excited to add these assets to our portfolio and to accelerate their development as we seek to deliver more treatments for cancer patients," said Giovanni Caforio, Chief Executive Officer and Board Chair, Bristol Myers Squibb. "With a strong strategic fit, great science and clear value creation opportunities for our shareholders, the Mirati transaction is aligned with our business development goals. Importantly, by leveraging our skills and capabilities, including our global commercial infrastructure, we will ensure patients globally can benefit from Mirati's portfolio of innovative medicines."

"With multiple targeted oncology assets including KRAZATI, Mirati is another important step forward in our efforts to grow our diversified oncology portfolio and further strengthen Bristol Myers Squibb's pipeline for the latter half of the decade and beyond," said Chris Boerner, Ph.D., Executive Vice President and Chief Operating Officer and Chief Executive Officer-Elect, Bristol Myers Squibb. "Today's news builds upon our long legacy of delivering breakthrough therapies that transform the lives of people with cancer. We are impressed with the science that the talented people of Mirati have driven in service of patients, and we look forward to welcoming them to Bristol Myers Squibb."

Source: https://news.bms.com/news/details/2023/Bristol-Myers-Squibb-Strengthens-and-Diversifies-Oncology-Portfolio-With-Acquisition-of-Mirati-Therapeutics/default.aspx

# Lilly to Acquire POINT Biopharma to Expand into Next-Generation Radioligand Therapies

**October 3, 2023 /PR NEWSWIRE/** -- Eli Lilly and Company (NYSE: LLY) and POINT Biopharma Global, Inc. (NASDAQ: PNT) today announced a definitive agreement for Lilly to acquire POINT, a radiopharmaceutical company with a pipeline of clinical and preclinical-stage radioligand therapies in development for the treatment of cancer. Radioligand therapy can enable the precise targeting of cancer by linking a radioisotope to a targeting molecule that delivers radiation directly to cancer cells, enabling significant anti-tumor efficacy while limiting the impact to healthy tissue.

POINT's lead programs are in late-phase development. PNT20021 is a prostate-specific membrane antigen (PSMA) targeted radioligand therapy in development for patients with metastatic castration-resistant prostate cancer (mCRPC) after progression on hormonal treatment. Topline data from this study are expected in the fourth quarter of 2023. PNT20031 is a somatostatin receptor (SSTR) targeted radioligand therapy in development for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Beyond the late-stage clinical pipeline, POINT has several additional programs in earlier stages of clinical and preclinical development. Additionally, POINT operates a 180,000-square-foot radiopharmaceutical manufacturing campus in Indianapolis, as well as a radiopharmaceutical research and development center in Toronto. These facilities will be utilized alongside POINT's extensive network of supply chain partners for sourcing radioisotopes and their precursors.

Lilly will commence a tender offer to acquire all outstanding shares of POINT for a purchase price of $12.50 per share in cash (an aggregate of approximately $1.4 billion) payable at closing. The transaction has been approved by the boards of directors of both companies.

The transaction is not subject to any financing condition and is expected to close near the end of 2023, subject to customary closing conditions, including the tender of a majority of the outstanding shares of POINT's common stock, and license transfer approval from the U.S. Nuclear Regulatory Commission. Following the successful closing of the tender offer, Lilly will acquire any shares of POINT that are not tendered in the tender offer through a second-step merger at the same consideration as paid in the tender offer.

The purchase price payable at closing represents a premium of approximately 87% to POINT's closing stock price on Oct. 2, 2023, the last trading day before the announcement of the transaction, and 68% to the 30-day volume-weighted average price. POINT's board of directors unanimously recommends that POINT's stockholders tender their shares in the tender offer.

Source: https://www.prnewswire.com/news-releases/lilly-to-acquire-point-biopharma-to-expand-oncology-capabilities-into-next-generation-radioligand-therapies-301945243.html

## Kyowa Kirin to Acquire Orchard Therapeutics

*-Orchard Therapeutics is a global gene therapy leader with experience successfully developing and commercializing medicines for rare diseases-*
*-Acquisition enriches Kyowa Kirin's portfolio, enables the development of numerous promising candidates with a clinically differentiated platform, and helps resource the ongoing and future launches of Libmeldy® (atidarsagene autotemcel)-*
*-Acquisition price of $16.00 per ADS in cash plus an additional contingent value right of $1.00 per ADS, representing a total maximum equity value of approximately $477.6 million-*
*-Kyowa Kirin to host investor conference call on Oct 5 at 18:30 p.m. JST-*

**Tokyo, London and Boston, October 5, 2023,** — Kyowa Kirin Co., Ltd. (Kyowa Kirin, TSE: 4151) a Japan-based global specialty pharmaceutical company (J-GSP) creating innovative medical solutions utilizing the latest biotechnology, and Orchard Therapeutics plc (Orchard Therapeutics, Nasdaq: ORTX), a global gene therapy leader, today announced the companies have entered into a definitive agreement under which Kyowa Kirin will acquire Orchard Therapeutics for $16.00 per American Depositary Share (ADS) in cash (approximately $387.4 million, or ¥57.3 billion), under which Orchard shareholders will hold an additional contingent value right (CVR) of $1.00 per ADS. An additional $1.00 CVR will be paid for a total of $17.00 per ADS, or approximately $477.6 million (¥70.7 billion) if the conditions are met.

Kyowa Kirin's Thursday acquisition of Orchard Therapeutics for $387 million was the second major biopharma acquisition last week.

Orchard Therapeutics' portfolio includes Libmeldy® (atidarsagene autotemcel), intended for eligible patients with early-onset metachromatic leukodystrophy (MLD), a rare inherited disease of the body's metabolic system. In the most severe form of MLD, babies develop normally but in late infancy start to rapidly lose the ability to walk, talk and interact with the world around them. Libmeldy is approved by the European Commission (EC) and has an upcoming PDUFA date in the United States.

Source: https://t.co/TpPR00wa0x

# AbbVie to Acquire Mitokinin For $110 Million

**NORTH CHICAGO, Ill., Oct. 5, 2023 /PRNewswire/** -- AbbVie (NYSE: ABBV) announced today that it has exercised its exclusive right and completed the acquisition of Mitokinin, a discovery-stage biotechnology company developing a potentially first-in-class disease-modifying treatment for Parkinson's Disease (PD). Mitokinin's lead compound, a selective PINK1 activator, is designed to address mitochondrial dysfunction that is believed to be a major contributing factor to Parkinson's disease pathogenesis and progression.

PINK1 plays a key role in maintaining a healthy mitochondrial system by facilitating the turnover of dysfunctional mitochondria. Mutations in PINK1 are associated with a loss of PINK1 function and cause familial forms of PD. Activation of PINK1 offers a potentially disease-modifying treatment approach beyond familial PD, by addressing mitochondrial dysfunction and improving mitochondrial health in sporadic PD.

"Parkinson's disease continues to be a major unmet medical need, impacting patients, caregivers and society. With this acquisition, we are excited to grow our neuroscience portfolio and explore a potential new treatment option for PD," said Jonathon Sedgwick, Ph.D., vice president and global head of discovery research, AbbVie. "While current PD treatments may alleviate the symptoms of parkinsonism, there are currently no available therapies that prevent progression of the disease. Targeting PINK1 offers a novel approach that may alter disease pathogenesis."

"Collaboration with AbbVie's world-class Neuroscience and External Innovation teams added significant value and resources to help accelerate the program to investigational new drug (IND) enabling studies," said Daniel de Roulet, co-founder and chief executive officer, Mitokinin.

The role of PINK1 in addressing mitochondrial dysfunction has long been recognized; however, developing selective, brain penetrant PINK1 activators for therapeutic use in PD has been challenging. "Our pre-clinical data demonstrate that our PINK1 activator compound can selectively enhance the active-form of PINK1, which is found on damaged mitochondria, without impacting PINK-1 regulation broadly," said Nicholas Hertz, Ph.D., co-founder and chief scientific officer, Mitokinin. "We believe this approach could potentially deliver significant clinical benefit to Parkinson's patients."

Under the terms of the agreement, AbbVie will pay Mitokinin shareholders $110 million at closing for the acquisition of Mitokinin. Mitokinin shareholders remain eligible for potential additional payments of up to $545 million upon the achievement of certain development and commercial milestones related to the success of the PINK1 program, plus tiered royalties based on net sales.

Source: https://news.abbvie.com/news/press-releases/abbvie-exercises-exclusive-right-to-acquire-mitokinin-further-strengthening-neuroscience-pipeline.htm

# Sanofi Pays $500mm Upfront to Collaborate with Teva on TLA1

**PARIS & PARSIPPANY, N.J--(BUSINESS WIRE) – October 4, 2023**-- Sanofi (EURONEXT: SAN and NASDAQ: SNY) and Teva Pharmaceuticals, a U.S. subsidiary of Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) announce today a collaboration to co-develop and co-commercialize asset TEV '574, currently in Phase 2b clinical trials for the treatment of Ulcerative Colitis and Crohn's Disease, two types of inflammatory bowel disease.

***Paul Hudson,*** Chief Executive Officer, Sanofi: *"Anti-TL1As are a promising class of therapies, and we believe that TEV '574 could emerge as a best-in-class option for people living with serious gastrointestinal diseases. This collaboration strengthens our commitment to advancing innovative treatment options for inflammatory conditions with a high unmet need and bolsters our goal to be an industry leader in immunology."*

***Richard Francis,*** President and Chief Executive Officer, Teva: *"This is a new era for Teva, and our robust, innovative pipeline is key to our Pivot to Growth strategy. This collaboration further validates the great science that Teva has to offer with our internally developed anti-TL1A*

Under the terms of the new collaboration agreement, Teva will receive an upfront payment of €469 million ($500 million) and up to €940 million ($1 billion) in development and launch milestones. Each company will equally share the development costs globally and net profits and losses in major markets, with other markets subject to a royalty arrangement and Sanofi will lead the development of the Phase 3 program. Teva will lead commercialization of the product in Europe, Israel and specified other countries, and Sanofi will lead commercialization in North America, Japan, other parts of Asia and the rest of the world.

Source: https://ir.tevapharm.com/news-and-events/press-releases/press-release-details/2023/Sanofi-and-Teva-Announce-Exclusive-Collaboration-to-Deliver-Inflammatory-Bowel-Disease-Treatment/default.aspx

# Sanofi Pays $175 Million Upfront to J&J for License to E. Coli Vaccine in Phase 3

**PARIS, Oct. 3, 2023** -- Sanofi announces today that it has entered into an agreement with Janssen Pharmaceuticals, Inc. (Janssen), a Johnson & Johnson company, to develop and commercialize the vaccine candidate for extraintestinal pathogenic E. coli (9-valent) developed by Janssen, currently in Phase 3. The agreement brings together Janssen's robust science behind this potential first-in-class product and Sanofi's worldwide manufacturing footprint and recognized world-class expertise in launching innovative vaccines.

Thomas Triomphe, Executive Vice President, Vaccines, Sanofi said:

> *"E. coli is a significant cause of sepsis, mortality, and antimicrobial resistance in older adults, and the number of cases is rising as the population ages. In line with our commitment to design and deliver first- or best-in-class medicines and vaccines, this agreement with Janssen aims to positively impact public health by reducing hospitalization costs and the burden on health systems associated with ExPEC and help older adults around the world to live longer, healthier lives."*

Under the terms of the agreement, both parties will co-fund current and future research and development costs. Sanofi will pay USD 175M upfront to Janssen, followed by development and commercial milestones. There will be a profit-share arrangement in the U.S., EU4 (France, Germany, Italy, Spain), and the UK. In the rest of the world (ROW), Janssen will receive tiered royalties and sales milestones. Closing is subject to customary regulatory clearance.

Extraintestinal pathogenic E. coli is a leading cause of sepsis, particularly in older adults3. Sepsis is a life-threatening bloodstream infection accompanied by severe illness and widespread organ damage, generated by the body's self-destructive response to the infection. The main risk factors include age, especially 60+, and chronic illnesses (e.g., diabetes, cancer, or kidney disease). Antimicrobial resistant (AMR) E. coli strains are an ongoing healthcare concern, with extraintestinal pathogenic E. coli a major driver behind the global AMR crisis4.

The ongoing Phase 3 E.mbrace trial is designed to evaluate the efficacy of the 9-valent extraintestinal pathogenic E. coli vaccine (ExPEC9V) compared to placebo in the prevention of invasive E. coli disease (IED) caused by ExPEC9V O-serotypes. The study was started in 2021 by Janssen and continues to enroll patients.

Source: https://newsroom.viatris.com/2023-10-01-Viatris-Announces-Agreements-on-Remaining-Planned-Divestitures-Upon-Closing-Would-Achieve-its-Original-Total-Target-of-a-Multiple-Above-12x-on-2022-Estimated-Adjusted-EBITDA

# Viatris Announces Agreements on Remaining Planned Divestitures; Upon Closing Would Achieve its Original Total Target of a Multiple Above 12x on 2022 Estimated Adjusted EBITDA

**PITTSBURGH, Oct. 1, 2023 /PRNewswire/** -- Viatris Inc. (NASDAQ: VTRS), a global healthcare company, today announced it has received an offer for the divestiture of substantially all of its Over-the-Counter (OTC) business, and has entered into definitive agreements to divest its Women's Healthcare business, its Active Pharmaceutical Ingredients (API) business in India and commercialization rights in certain non-core markets that were acquired as part of the Upjohn Transaction.

Viatris CEO Scott A. Smith said: "I am very excited about today's announcement as it marks an important milestone in the execution of our overall strategic plan. Not only will this bring to conclusion all of our Phase 1 commitments, including the expected achievement of our deleveraging target of 3 times gross leverage in the first half of 2024, importantly it will also set the Company up extremely well as we enter into our Phase 2 strategy for 2024 and beyond.

Smith continued: "Since joining Viatris, I have had the opportunity to review these divestitures more closely.  After taking this closer look, I have made the decision to retain our rights for Viagra and Dymista, as well as other select OTC assets within certain markets as we see further opportunities for these products within Viatris. Needless to say, I am extremely pleased with our excellent overall results — reaching the Company's previously communicated range on both aggregate value and multiple while also retaining important assets — despite the challenging external macro-economic environment in which we had to execute. In addition, we achieved our goal of substantially simplifying the organization as we increase our focus on areas with the greatest potential to accelerate our growth, patient impact and shareholder value. We are committed to ensuring a successful transition for our colleagues, our partners, our customers and the patients we serve."

*Total Divestitures Summary*

With this announcement the Company has delivered on its commitment to announce agreements on all planned divestitures by the end of 2023 within the Company's previously communicated range, after considering the estimated retained value. Including gross proceeds from the Company's completed biosimilars divestiture, the Company expects to realize gross proceeds representing a multiple above 12x on 2022 estimated Adjusted EBITDA for its portfolio of divested assets. The gross proceeds to the Company from all divestitures under the terms of the agreements are up to $6.94 billion, or up to approximately $5.2 billion in estimated aggregate net proceeds, taking into consideration taxes and other costs, including related transaction costs. The Company made the strategic decision to retain rights for Viagra®, Dymista®, and select OTC products in certain markets representing estimated retained value of approximately $1.6 billion applying the OTC multiple of 12.8x to the 2022 estimated Adjusted EBITDA of $125 million attributable to the retained business. Total gross proceeds from all planned divestitures and estimated retained value are in line with the Company's previously communicated range. Viatris intends to prioritize the use of net proceeds from the divestitures for debt paydown. The application of such proceeds is expected to achieve a gross leverage target of 3.0x in the first half of 2024, completing all Viatris' Phase 1 commitments which the Company believes will position it to accelerate growth and increase shareholder return as it enters Phase 2 of its strategic plan in 2024. In addition, the Company expects that completing the divestitures would substantially simplify the organization. Under the terms of the today's announced divestitures, up to12 facilities and more than 6,000 employees, representing 15 percent of the Company's global workforce, may be conveyed.

Source: https://newsroom.viatris.com/2023-10-01-Viatris-Announces-Agreements-on-Remaining-Planned-Divestitures-Upon-Closing-Would-Achieve-its-Original-Total-Target-of-a-Multiple-Above-12x-on-2022-Estimated-Adjusted-EBITDA

# Viatris Announces Agreements on Remaining Planned Divestitures (continued)

## Overview of the Transactions

The transactions are subject to regulatory approvals, completion of any consultations with employee representatives (where applicable), receipt of required consents and other closing conditions, including, in the case of the API business divestiture, a financing condition.

Viatris has received an offer from Cooper Consumer Health, a leading European over-the-counter drug manufacturer and distributor. Subject to the completion of consultations with applicable works councils, the offer grants Viatris the right to divest substantially all of its OTC business, including two manufacturing sites located in Merignac, France, and Confienza, Italy, and a Research & Development (R&D) site in Monza, Italy. The Company will retain rights for Viagra®, Dymista® and select OTC products in certain markets. The transaction would be expected to close in Q2 2024.

Viatris has executed an agreement to divest its API business in India to Iquest Enterprises, a privately held pharmaceutical company, also based in India. The transaction includes three manufacturing sites and a R&D lab in Hyderabad, three manufacturing sites in Vizag and third-party API sales. Viatris will retain some selective R&D capabilities in API. The transaction is expected to close in Q1 2024.

Viatris has also executed an agreement to divest its Women's Healthcare business, primarily related to oral and injectable contraceptives, to Insud Pharma, a leading Spanish multinational pharmaceutical company. The transaction includes two manufacturing facilities in India: one in Ahmedabad and one in Sarigam. The transaction is expected to close in Q1 2024.

Separately, in another transaction, Viatris entered into an agreement to divest its rights to women's healthcare products Duphaston® and Femoston® to Theramex, a leading global specialty pharmaceutical company dedicated to women's health. The transaction is expected to close in Q4 2023.

Viatris has also executed agreements to divest commercialization rights in certain non-core markets that were part of the combination with Upjohn in which the Company had no established infrastructure prior to or following the transaction. These transactions are expected to be completed in Q4 2023.

Source: https://newsroom.viatris.com/2023-10-01-Viatris-Announces-Agreements-on-Remaining-Planned-Divestitures-Upon-Closing-Would-Achieve-its-Original-Total-Target-of-a-Multiple-Above-12x-on-2022-Estimated-Adjusted-EBITDA

# Viatris Announces Agreements on Remaining Planned Divestitures (continued)

## Total Divestitures Summary

| ($B) | Previous Range (November 7, 2022) | Total Estimated Transaction Value | Estimated Retained Value | Total Estimated Transaction and Retained Value |
|---|---|---|---|---|
| Biosimilars (1) | $3.335 | $3.335 | | $3.335 |
| Other Non-core Assets (1)(2) | ~$5.0 - $6.0 | ~$3.6 | ~$1.6 | ~$5.2 |
| Total Pre-tax Proceeds | **~$8.3 - $9.3** | ~$6.94 | ~$1.6 | **~$8.5** |
| Estimated Net Proceeds | **~$4.9 - $6.1** | ~$5.2 (3) | ~$1.2 | **~$5.7** (4) |

Note: For non-GAAP measures, see slide 3

(1) Estimated 2022 revenues and adjusted EBITDA from all divested assets of ~$2.0B and ~$0.56B, respectively, inclusive of estimated 2022 revenues and adjusted EBITDA from Other Non-core Assets of ~$1.3B and ~$0.39B, respectively.

(2) Other Non-core Assets include OTC, API, Women's Healthcare, and Non-Core Markets acquired as part of the Upjohn transaction.

(3) Estimated Net Proceeds from Other Non-core Assets of ~$2.55B.

(4) Estimated Net Proceeds of ~$5.7B was calculated as the estimated net proceeds from all divestitures of ~$5.2B plus the estimated retained value of ~$1.2B less the eye care acquisition of ~$0.7B.

Source: https://newsroom.viatris.com/2023-10-01-Viatris-Announces-Agreements-on-Remaining-Planned-Divestitures-Upon-Closing-Would-Achieve-its-Original-Total-Target-of-a-Multiple-Above-12x-on-2022-Estimated-Adjusted-EBITDA

# Eli Lilly: Point Acquisition Gives Battered Biotech Sector a Boost

**Lex, *Financial Times*, October 3, 2023 (excerpt)**

These are tough times to be a biotech company — and an investor in one. Confidence has collapsed. Higher interest rates have dulled risk appetites and dried up funding.

Eli Lilly's $1.4bn acquisition of Point Biopharma Global is good news for the battered sector. Cheaper valuations have finally drawn cash-rich pharmaceutical makers back to biotechs. Their aim, as always, is to replenish their drug pipelines affordably. Relief is sorely needed. The market worth of some publicly listed biotechs is now less than their cash reserves. The Nasdaq Biotechnology index has crashed nearly a third from its 2021 peaks. A once-popular fund, the SPDR S&P Biotech ETF, has lost 14 per cent of its value this year, falling 60 per cent from its highs.

Eli Lilly's $12.50 a share cash offer for Point represents a 50 per cent premium to the stock's undisturbed three month average. That may appear steep for a company without any approved drugs, or any revenues. It looks less alarming when you consider that Point shares traded above $16 two and a half years ago. In addition, Point held about $434.8mn in cash, cash equivalents and investments at the end of June. This is a very small deal for a company as big as Eli Lilly. The drugs giant is riding high on diabetes drug Mounjaro, which has potential use as a weight-loss treatment. It is also seeking a bigger presence in treating cancer. Point has a promising experimental treatment here. There is no better time to buy than in the wake of an asset bubble popping.

This was inflated by low interest rates and a boom for life science companies during Covid-19. The peak came in 2021 with more than 100 biotechs going public, raising nearly $15bn in total. Most will not be acquired by larger pharma groups. Bold investors with some pharma knowledge should consider stock picking, rather than passively investing in biotech indices. Look out for promising treatments that appear on track for approval. Big pharma is playing the same game.

Source: https://www.ft.com/content/c9f56bff-6ddd-4034-924e-bf5077f6334b

# Pharma Industry Plays Defense on Merger Guidelines

**Mary Goldman, Axios, October 4, 2023 (excerpt)**

Pharmaceutical giants including Amgen, Merck and Gilead formed a coalition Wednesday to push back against a proposed overhaul of federal antitrust guidelines.

**Why it matters:** In health care, much of the discussion around the tougher merger rules so far has focused on how they might slow down a wave of provider consolidation. But the new coalition, the Partnership for the U.S. Life Science Ecosystem, argues the antitrust proposal would choke off a key source of innovation, since mergers and acquisitions are often the only way for biopharma startups to advance their treatments.

The Federal Trade Commission and the Justice Department in July proposed changes to merger guidelines that could broadly affect a range of deals, as the Biden administration signaled an era of more aggressive enforcement. The agencies also proposed new premerger requirements.

Source: https://www.axios.com/2023/10/04/pharma-ftc-doj-mergers

# List of Biopharma Companies Exploring Strategic Options

| Ticker | Company | Announcement Date | Last Cash ($mm) | Enterprise Value ($mm) | Note |
|---|---|---|---|---|---|
| IMPL | Impel Pharmaceuticals | 10/5/2023 | $15.2 | $103.5 | Highly leveraged. Kicking off process. Commercial product. |
| GLTO | Galecto | 9/26/2023 | $52.1 | -$33.4 | Full pipeline. Executed large layoff. |
| ARAV | Aravive | 8/21/2023 | $18.4 | -$6.3 | |
| GRTX | Galera Therapeutics | 8/14/2023 | $38.8 | $118.3 | Can deliver $5 to 10mm cash |
| TCRT | Alaunos Therapeutics | 8/14/2023 | $18.3 | $9.9 | |
| SLRX | Salarius Pharmaceuticals | 8/8/2023 | $11.5 | -$9.1 | |
| NBSE | Neubase | 8/3/2023 | $13.8 | -$6.3 | |
| AVTX | Avalo Therapeutics | 8/3/2023 | $6.3 | $36.8 | |
| VXL | Vaxil Bio | 8/2/2023 | $0.8 | $0.7 | |
| FIXX | Homology Medicines | 7/27/2023 | $127.1 | -$34.2 | No recent updates |
| SQZB | SQZ Biotechnologies | 7/25/2023 | $24.7 | -$0.7 | |
| ELYM | Eliem Therapeutics | 7/20/2023 | $102.6 | -$31.1 | No recent updates |
| RKDA | Arcadia Biosciences | 7/20/2023 | $18.5 | -$13.7 | |
| NMTR | 9 Meters | 7/19/2023 | $0.0 | $0.0 | In Bankruptcy. Ongoing auction |
| PIRS | Pieris Pharma | 7/18/2023 | $54.9 | -$11.2 | |
| AVRO | AvroBio | 7/12/2023 | $124.7 | -$51.9 | No recent updates |
| HSTO | Histogen | 7/5/2023 | $7.3 | -$0.6 | In Liquidation. Some assets. |
| RVLP | RVL Pharmaceuticals | 7/5/2023 | $19.2 | $53.1 | |
| SPEX | Spexis | 6/30/2023 | $1.0 | $25.5 | |
| AUPH | Aurinia Pharmaceuticals | 6/29/2023 | $350.4 | $797.8 | Process triggered by activist. Not necessarily a sale. |
| BLPH | Bellorophon Therapeutics | 6/24/2023 | $10.6 | -$5.9 | |
| ONCR | Oncorus | 6/1/2023 | $45.0 | $25.0 | |
| NOVN.Q | Novan | 5/31/2023 | $12.5 | $24.6 | In Bankruptcy. Loan from Ligand. Upcoming PDUFA date. |
| GMDA | Gamida Cell | 5/15/2023 | $54.1 | $169.1 | |
| IMVI.Q | IMV | 5/1/2023 | $21.2 | $7.8 | |
| INFI | Infinity Pharma | 3/28/2023 | $0.4 | $1.8 | In Bankruptcy |
| BLCM | Bellicum Therapeutics | 3/14/2023 | $7.4 | $22.5 | |
| FRTX | Fresh Tracks Therapeutics | 3/7/2023 | $8.9 | -$2.9 | In Bankruptcy |
| GRPH | Graphite Bio | 2/23/2023 | $284.0 | -$152.0 | Has not updated on process for over 9 months. |
| EVFM | Evofem Biosciences | 2/23/2023 | $7.7 | $81.0 | Has commercial product. |
| ALRN | Aileron | 2/21/2023 | $13.7 | -$7.2 | |
| GTTX | Genetether | 2/8/2023 | $2.0 | $1.0 | |
| AXLA | Axcella Therapeutics | 12/14/2022 | $8.9 | $22.0 | Rich pipeline |
| MEIP | MEI Pharma | 12/6/2022 | $100.7 | -$42.3 | Activist involvement. |
| SNGX | Soligenix | 11/10/2022 | $17.0 | $4.0 | |
| HGEN | Humanigen | 10/31/2022 | $3.1 | -$1.7 | |
| XCUR | Exicure | 9/26/2022 | $15.6 | -$3.0 | In Liquidation |
| TENX | Tenax Therapeutics | 9/14/2022 | $13.4 | -$6.5 | |
| GLMD | Galmed | 6/15/2022 | $22.4 | -$12.0 | |
| ABIO | Arca Bio | 4/18/2022 | $43.9 | -$12.0 | Long running process. Activist in situation. |
| ADMA | ADMA Biologics | 10/21/2021 | $62.5 | $842.4 | Commercial stage company. Long process. |

Source: Stifel Research

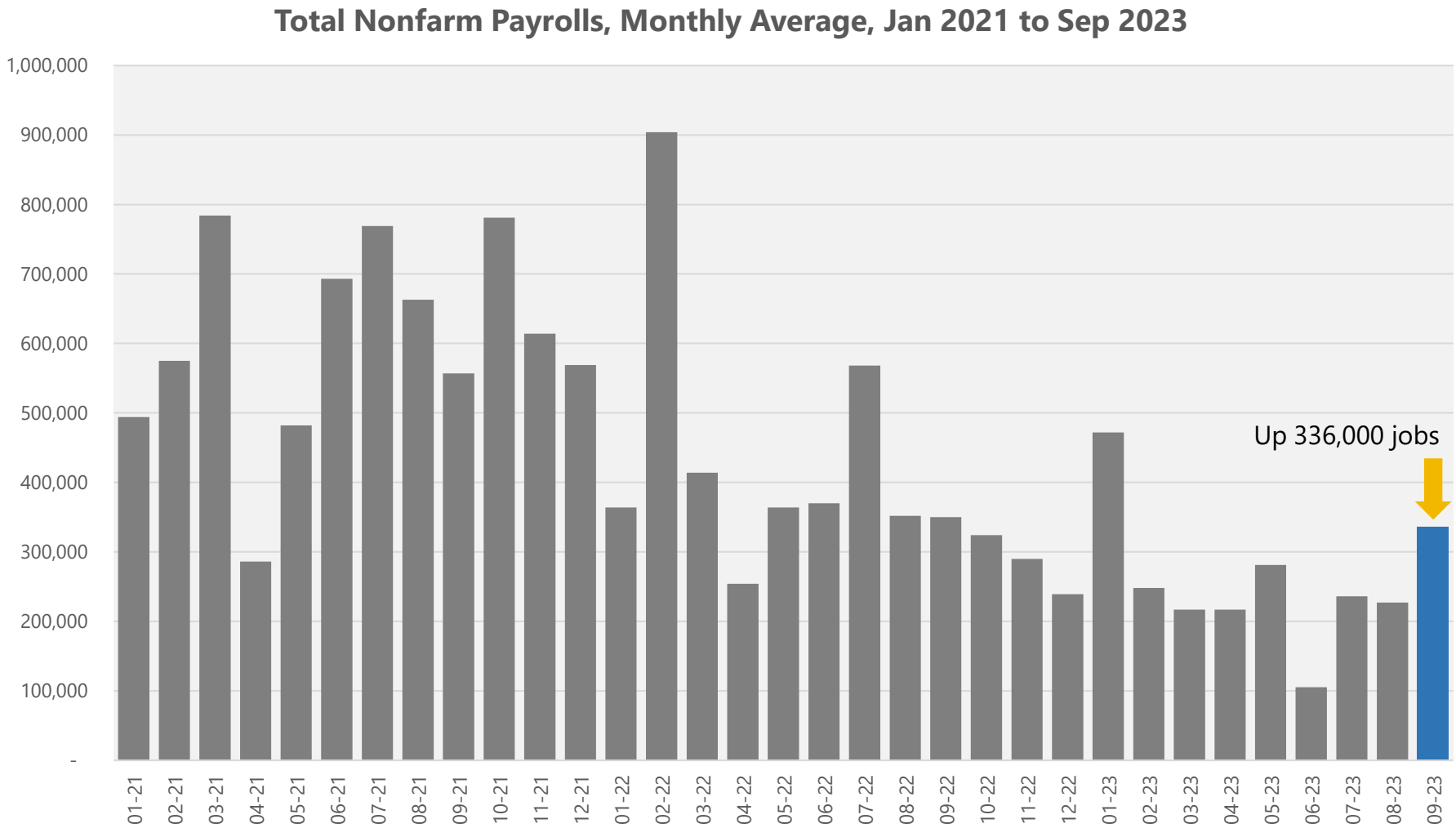
**We count an unprecedented 41 biopharma companies that have publicly indicated that they are exploring strategic options.**

**A number of these companies are in a formal liquidation or bankruptcy process.**

# Macro Update

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

# Robust U.S. Jobs Data Last Friday




The September jobs report went against expectations from many. The U.S. economy remains strong and added more jobs in a month than in any month but one in the last year.

We're supposed to be teetering on the brink of a recession.

That's obviously *not* in the cards. At least for now.

Source: https://www.bls.gov/news.release/empsit.nr0.htm

# Jobs Gains Surge, Troubling News for the Federal Reserve

**Jenna Smialek, *New York Times*, October 6, 2023 (excerpt)**


Federal Reserve officials are likely to cast a wary eye on September jobs data, which showed that employers both hired at a rapid clip last month and had added more workers in the previous two months than had been reported earlier.

Employers added 336,000 jobs last month, sharply more than the 170,000 economists had predicted. Fed officials have been keeping a careful watch on the labor market as they try to assess how much more they need to raise interest rates to bring inflation under control, and how long borrowing costs should stay high.

Central bankers had been encouraged as job growth had cooled without collapsing in recent months. They have continued to predict that unemployment will probably rise slightly as the economy slows: To about 4.1 percent, which would still be low by historical standards. Unemployment stood at 3.8 percent as of September.

"Although the jobs-to-workers gap has narrowed, labor demand still exceeds the supply of available workers," Jerome H. Powell, the Fed chair, said during a news conference in mid-September. Fed officials "expect the rebalancing in the labor market to continue, easing upward pressures on inflation."

# U.S. Treasury Borrowing Heavily Through September

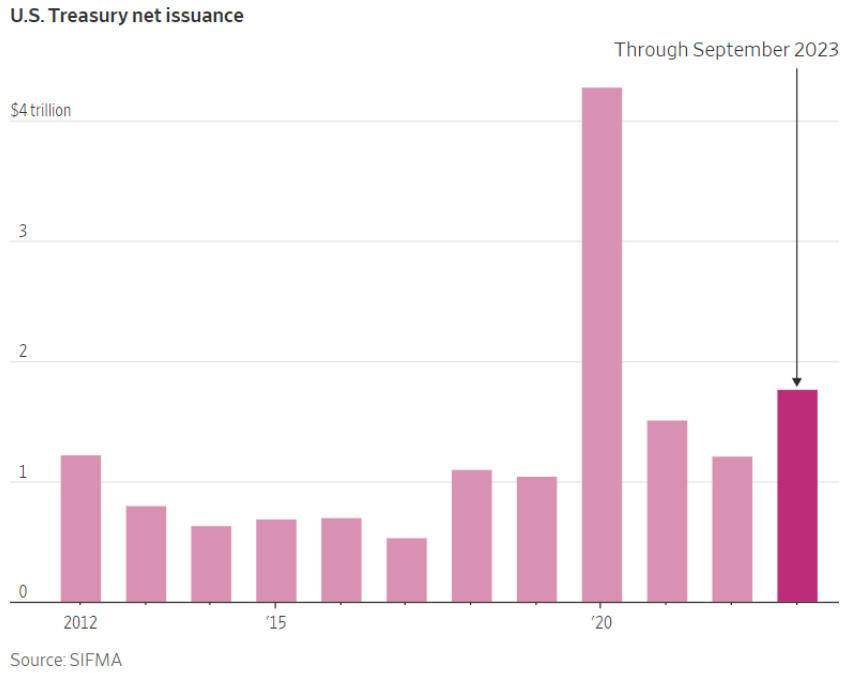
**Eric Wallerstein, *Wall Street Journal*, October 8, 2023 (excerpt)**

Ever since the Federal Reserve broke the inflation scare of the 1980s, Wall Street and Washington have shrugged off multitrillion-dollar deficits, counting on America's global standing to provide perpetual demand for its debt that could finance the spending. Now, the steep declines in prices of Treasurys—meant to be the world's safest and easiest-to-trade investment—are forcing markets to confront the possibility that the rates required to place all this debt will be higher than anyone expected.

The yield on the benchmark 10-year Treasury note, which rises when bond prices fall, briefly surged near 4.9% on Friday after the monthly jobs report showed U.S. employers hired nearly double the workers that economists were anticipating. The strength of the labor market is one reason bond yields have soared this year, reflecting an improved outlook for economic growth and inflation.

Another came this summer, after the Treasury Department caught Wall Street off guard by announcing it would borrow roughly $1 trillion in the year's third quarter, more than a quarter trillion dollars above previous expectations. Already more than $1.76 trillion of Treasurys has been issued on a net basis through September, higher than in any full year in the past decade, excluding 2020's pandemic surge.

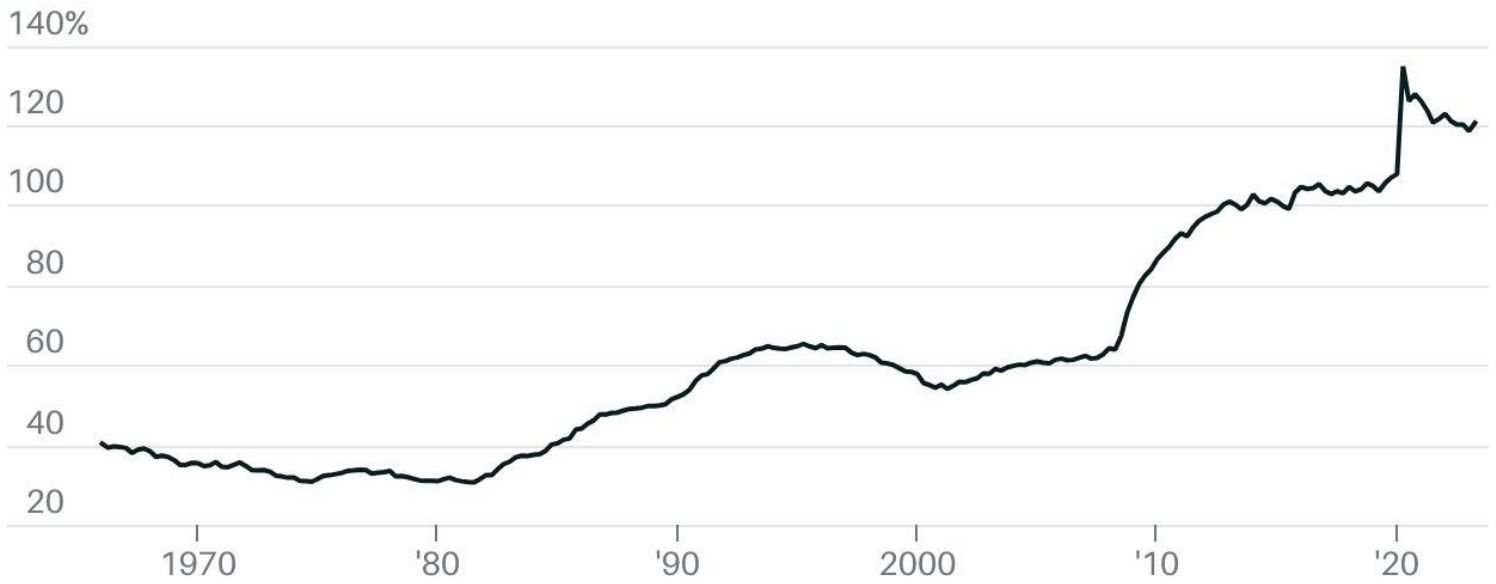
"The rise in bond yields has been relentless, and the price action has become disorderly," said Sophia Drossos, an economist and strategist at Greenwich, Conn.-based hedge fund Point72.




Source: https://www.wsj.com/finance/investing/government-spending-hurting-bond-portfolio-8a063f39

# U.S. Treasury Borrowing Heavily in October

The U.S. debt-to-GDP ratio.




Source: Office of Management and Budget.

The US added another $33 billion of debt in one day last week.

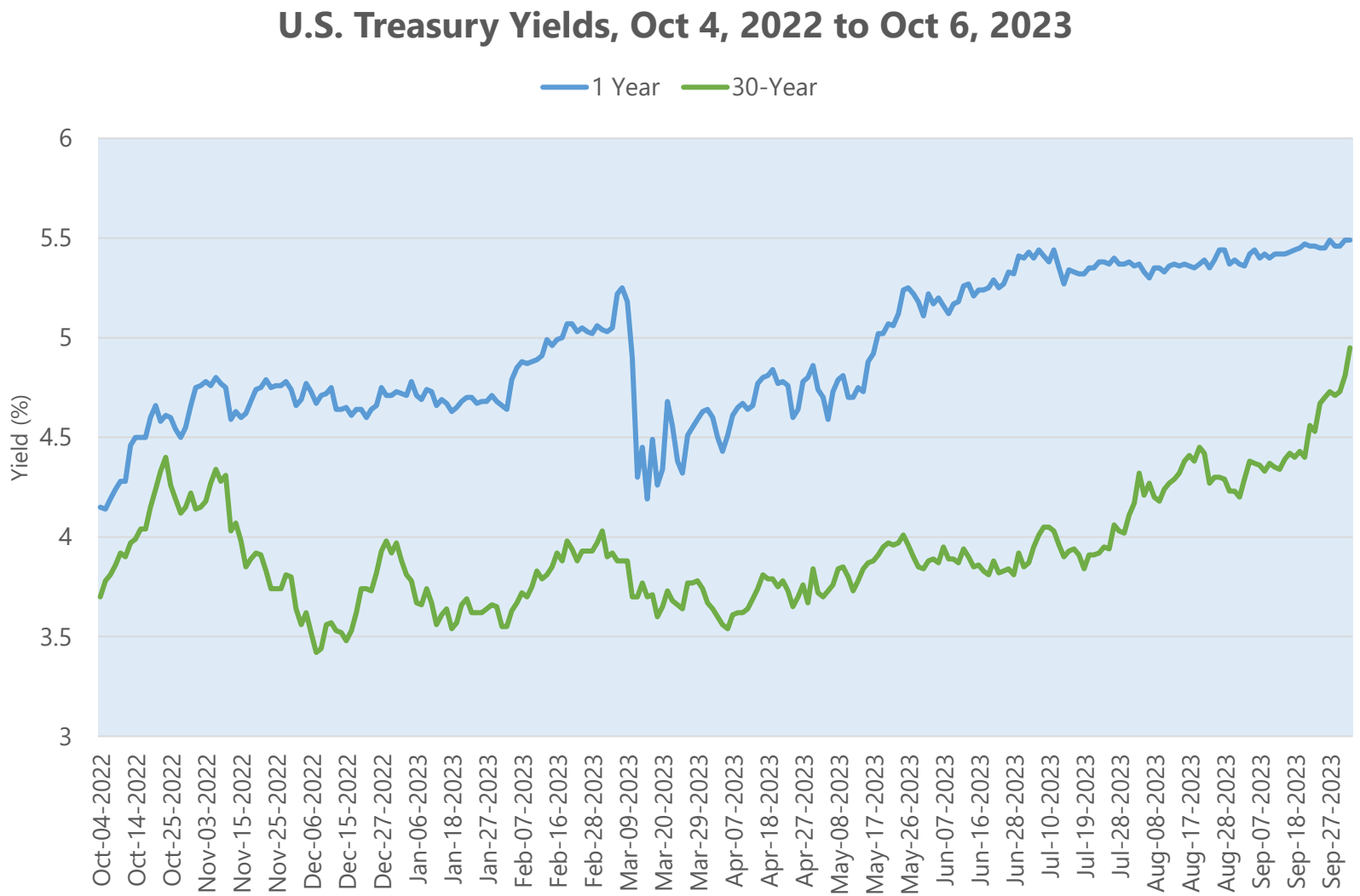
Since US debt crossed $33 trillion just 15 days ago, the US has added another ~$500 billion in debt.

That's an average of $1.4 billion per hour for the last two weeks.

If US debt borrowed over the last 2 weeks alone was split by every taxpayer, it would be $3,000 per person.

The U.S. Debt to GDP is back above 120% while we may see $34 trillion in total US debt within a month.

# 30-Year U.S. Treasury Yield Hits 5% This Week




Source: CapitalIQ

The U.S. government has been borrowing $250 billion a day in the last several weeks – in anticipation of a potential debt ceiling problem at the end of November.

To put this in perspective, the entire global biotech sector is worth less than $250 billion at this point.

The pressure on rates has been extreme – with U.S. 30-year bond yields spiking to over 5% on October 3rd.

None of this is good for biotech. We saw the XBI last week drop to 72.2

# Rising Interest Rates Mean Deficits Really Matter

**Greg Ip, *Wall Street Journal*, Oct 5, 2023 (excerpt)**

The U.S. has long been the lender of last resort to the world. During the emerging-market panics of the 1990s, the global financial crisis of 2007-09 and the pandemic shutdown of 2020, it was the Treasury's unmatched capacity to borrow that came to the rescue.

Now, the Treasury itself is a source of risk. No, the U.S. isn't about to default or fail to sell enough bonds at its next auction. But the scale and upward trajectory of U.S. borrowing and absence of any political corrective now threaten markets and the economy in ways they haven't for at least a generation.

That's the takeaway from the sudden sharp rise in Treasury yields in recent weeks. The usual suspects can't explain it: The inflation picture has gotten marginally better, and the Federal Reserve has signaled it's nearly done raising rates.

Instead, most of the increase is due to the part of yields, called the term premium, which has nothing to do with inflation or short-term rates. Numerous factors affect the term premium, and rising government deficits are a prime suspect.

Investors looking for U.S. political will to rein in deficits would take note that both former President Donald Trump and President Biden, their parties' front-runners for the 2024 presidential nomination, have signed deficit-busting legislation and that both of their parties have pledged not to cut the two largest spending programs, Medicare and Social Security, or raise taxes on most households.

They would also notice that the Republican speaker of the House of Representatives was just ousted by rebels in his own party because he had passed a bipartisan spending bill to prevent the government from shutting down. True, the rebels wanted less spending. But shutdowns, Barclays noted, represent "erosion of governance." This isn't how a country trying to reassure the bond market acts.

Source: https://www.wsj.com/economy/central-banking/rising-interest-rates-mean-deficits-finally-matter-74249719

# Are Rising Bond Yields and Deficits a National Crisis?

**Eric Levitz, *New York Magazine*, Oct 4, 2023 (excerpt)**

During Barack Obama's first term, a bipartisan consensus held that America faced a looming debt crisis. As the Great Recession eroded tax revenues and an aging population pushed up Social Security and Medicare costs, the United States would need to tighten its belt or suffer a steadily deepening economic calamity.

Deficit hawks insisted that this threat was urgent; so urgent that the federal government needed to slash spending even amid nearly double-digit unemployment and low inflation. This agitation for austerity succeeded in dampening the recovery, effectively condemning the U.S. to a lost decade of needlessly high unemployment and low growth. But it did little to stem the rising tide of budget deficits. Under Donald Trump, Republicans enacted massive tax cuts and increases in federal spending. And yet, before the COVID pandemic, Washington's profligacy failed to generate any of the ruinous consequences that hawks had prophesied: Inflation remained, if anything, excessively low, and interest payments ate up a historically small share of national income.

And yet, if the deficit hawks have less political influence today than they did in 2009, they have a stronger substantive argument than they did in the Obama years.

The reason why Congress was able to increase deficits between 2009 and 2021 without increasing the fiscal burden of the national debt was that interest rates were low and falling for the bulk of that period.

But the post-COVID inflation (and the Federal Reserve's response to it) has changed the outlook on interest rates dramatically. On Tuesday, the yield on a ten-year U.S. Treasury bond jumped to 4.8 percent, its highest level since 2007. If interest rates remain anywhere near that perch for a sustained period of time, the implications for the nation's finances will be profound. According to the Manhattan Institute's Brian Reidl, **a single percentage point increase in America's long-run borrowing costs would have the same fiscal impact as creating a second Defense Department.**

This said, the deficit hawks' narrative is still misleading for a few reasons.

For one thing, the United States will never suffer a "debt crisis" as that term is conventionally understood. The U.S. prints its own currency. We cannot run out of dollars and therefore will never need to default on our debts. America is all but certain to remain one of the world's largest economies and most coveted consumer markets throughout this century. For these reasons, a Greece-style meltdown is not in the cards.

Furthermore, **the trajectory of future interest rates is a policy choice**. The Federal Reserve has the power to set benchmark interest rates and to shore up demand for U.S. debt on financial markets through bond purchases.

The key question, therefore, is about the long-term balance of supply and demand in the economy. More to the point, it is about how we wish to allocate our nation's scarce resources. The reason why rising federal deficits are concerning is not because they could propel America into a debt crisis, but rather because they reflect imprudent and unjust allocations of national wealth.

Source: https://nymag.com/intelligencer/2023/10/are-rising-bond-yields-and-deficits-a-national-crisis.html

# Who Feels The Pain From The Bond Sell-Off?

## *Financial Times*, Oct 5, 2023 (excerpt)

A sell-off in global bond markets has pushed borrowing costs to their highest levels in a decade or more.That means potentially heavy losses for banks, insurers, pension funds and asset managers that own trillions of dollars of sovereign and corporate debt after loading up in recent years.

Policymakers and investors are wary that the latest round of sharp moves could inflict severe damage on various parts of the financial system.

“We are watching this . . . very carefully to see if something breaks,” said Salman Ahmed, global head of macro at Fidelity International.

U.S. Banks: Paper losses on the most opaque part of US banks’ bond portfolios are now close to $400bn — an all-time high, and 10 per cent above the peak at the start of the year that caused the collapse of Silicon Valley Bank — according to Matthew Anderson, an analyst at bond data firm Trepp.

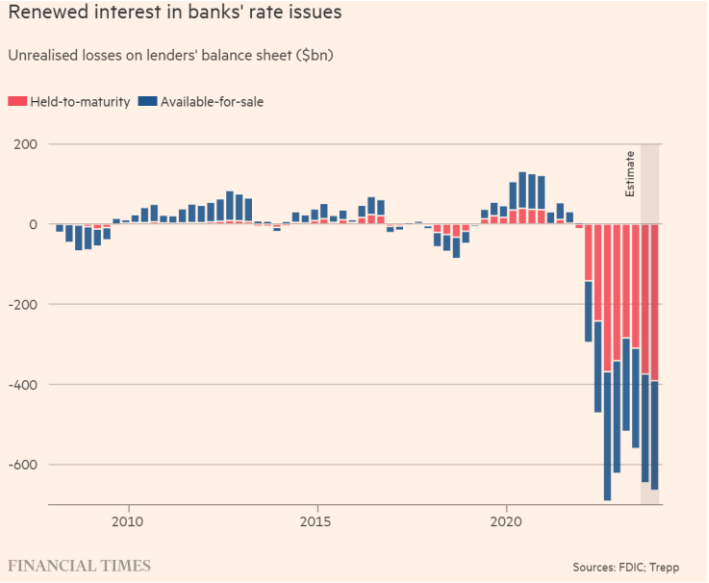
The results, published in July, showed the 104 banks supervised by the ECB had combined net unrealised losses of €73bn in their bond portfolios in February. The analysis showed that those losses would increase by an additional €155bn in the worst-case scenario of the regulator’s bank stress tests.

Corporate debt markets have also come under intensifying pressure from the sharp rise in government bond yields, which feeds through to companies’ borrowing costs. The average yield on US junk bonds climbed above 9.3 per cent this week, up from less than 9 per cent at the end of September and 8.5 per cent a month earlier.

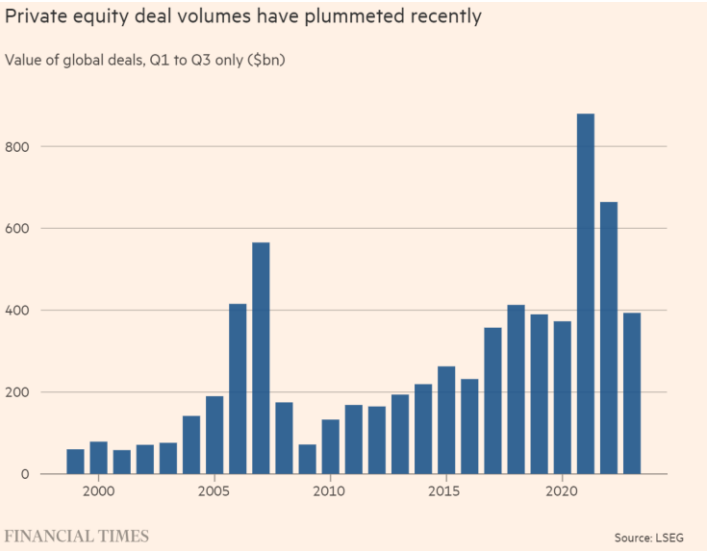
The prospect of interest rates staying higher for longer is bad news for private equity on multiple fronts. Dealmaking had already dropped over the past 12 months as buyout firms struggled with the impact of rising borrowing costs.

Source: https://www.ft.com/content/144c541a-1109-40c9-b74a-7d176ba90fc6

## Banks




## Private Equity



# Fresh Dose of Geopolitical Uncertainty

**Bloomberg, October 8, 2023 (excerpt)**

Global financial markets already rattled by elevated interest rates now face a fresh dose of geopolitical uncertainty following Hamas's surprise attack on Israel.

Saturday's strike and Israel's subsequent declaration of war risk unnerving markets when they reopen Monday, with investors eyeing the reaction of the oil price as a guidepost, although crude traders aren't anticipating an outsized surge.

Sentiment toward stocks could take a hit with IG's Weekend Wall Street contract down about 0.4% at noon on Sunday in London. Bond traders will need to quickly determine if the clash is a reason to rush for the safety of the dollar, shunning higher yielding-debt, or to fear yet another bout of inflation.

The fallout in markets will likely be determined by whether conflict spreads to the rest of the Middle East region. Iran is both major oil producer and supporter of Hamas.

"Geopolitical crises in the Middle East have usually caused oil prices to rise and stock prices to fall," said Ed Yardeni, president of Yardeni Research Inc. "Much will depend on whether the crisis turns out to be another short-term flare-up or something much bigger like a war between Israel and Iran."

Source: https://www.bloomberg.com/news/articles/2023-10-08/global-markets-face-new-geopolitical-risk-view-oil-as-guidepost

# Israeli War Could Impact Inflation / Oil

**Javier Blas, *Bloomberg* (opinion), October 7, 2023 (excerpt)**

History doesn't repeat itself, but it often rhymes. On the eve of the 50th anniversary of the world's first oil crisis, the parallels between October 2023 and October 1973 are easy to draw: A surprise attack on Israel and oil prices rising. But the resemblance ends there.

The global economy isn't about to suffer another Arab oil embargo that would triple the price of a barrel of crude. Yet, it would be a mistake to downplay the chances that the world faces higher-for-longer oil prices.

The situation is fluid, and for the oil market, everything depends about how Israel responds to Hamas, which launched the attack, and Iran, which typically pulls the strings of the Palestinian group. Still, we can draw a few tentative conclusions:

1) The crisis isn't a repeat of October 1973. Arab countries aren't attacking Israel in unison. Egypt, Jordan, Syria, Saudi Arabia and the rest of the Arab world are watching the events from the sidelines, not shaping them.

2) The oil market itself doesn't have any of the pre-October 1973 characteristics. Back then, oil demand was surging, and the world had exhausted all its spare production capacity. Today, consumption growth has moderated, and is likely to slow further as electric vehicles become a reality. In addition, Saudi Arabia and the United Arab Emirates have significant spare capacity that they use to curb prices – if they choose to do so.

Source: https://www.bloomberg.com/opinion/articles/2023-10-07/hamas-attack-on-israel-for-oil-it-s-not-1973-but-it-could-still-turn-ugly

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

# Biopharma Market Update

# Biotech Stocks Down Slightly Last Week

**The XBI was down only slightly last week despite a strong U.S. payrolls report and increasing interest rates.**

## Biotech Stocks Down Last Week

**Return: Sep 30 to Oct 6, 2023**

Nasdaq Biotech Index: 0.2%
Arca XBI ETF: -1.1%
Stifel Global Biotech (EV): -2.3%*
S&P 500: 0.5%

**Return: Jan 1 to Oct 6, 2023**

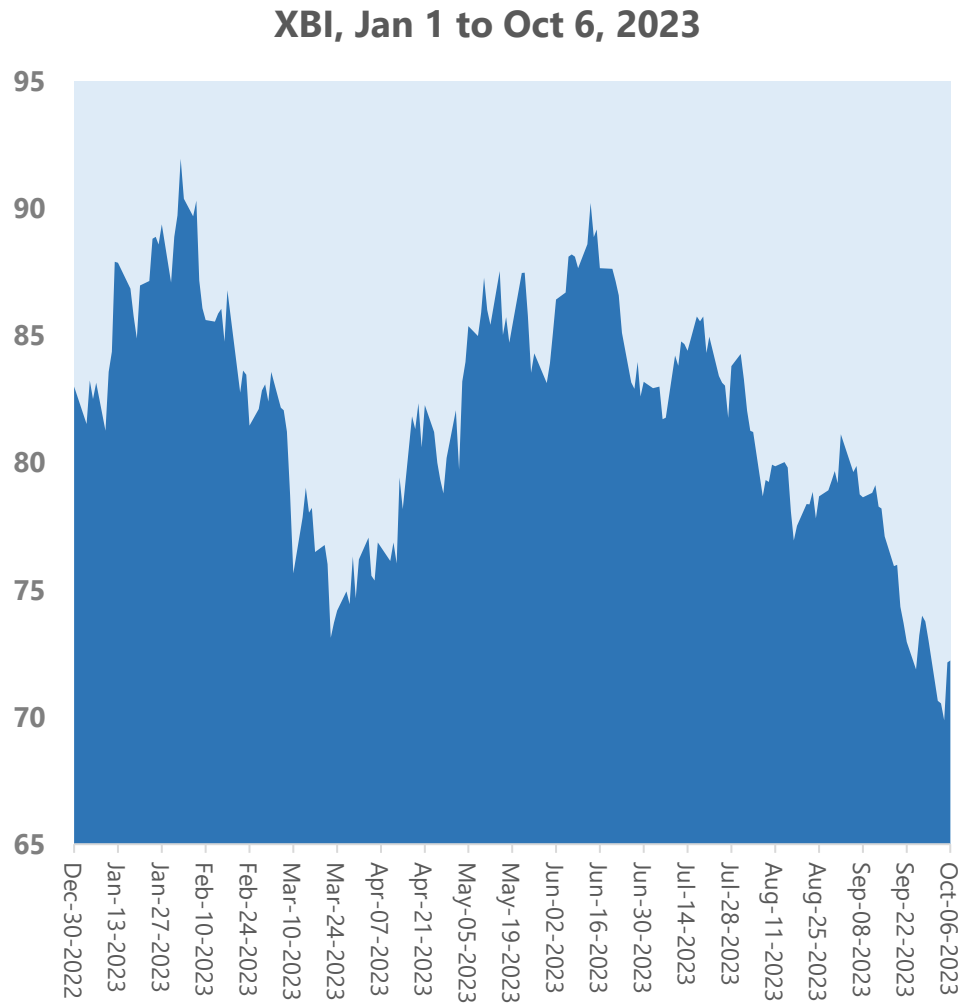
Nasdaq Biotech Index: -6.0%
Arca XBI ETF: -13.0%
Stifel Global Biotech: -15.6%*
Stifel Global Biotech (adjusted): -3.4%*
S&P 500: +12.2%

## VIX Up

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
May 26: 18.0%
July 21: 13.6%
Sep 8: 13.8%
Sep 29: 17.3%
Oct 6: 17.5%

## 10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
May 26: 3.8%
July 21: 3.84%
Sep 8: 4.26%
Sep 30: 4.59%
Oct 6: 4.78%

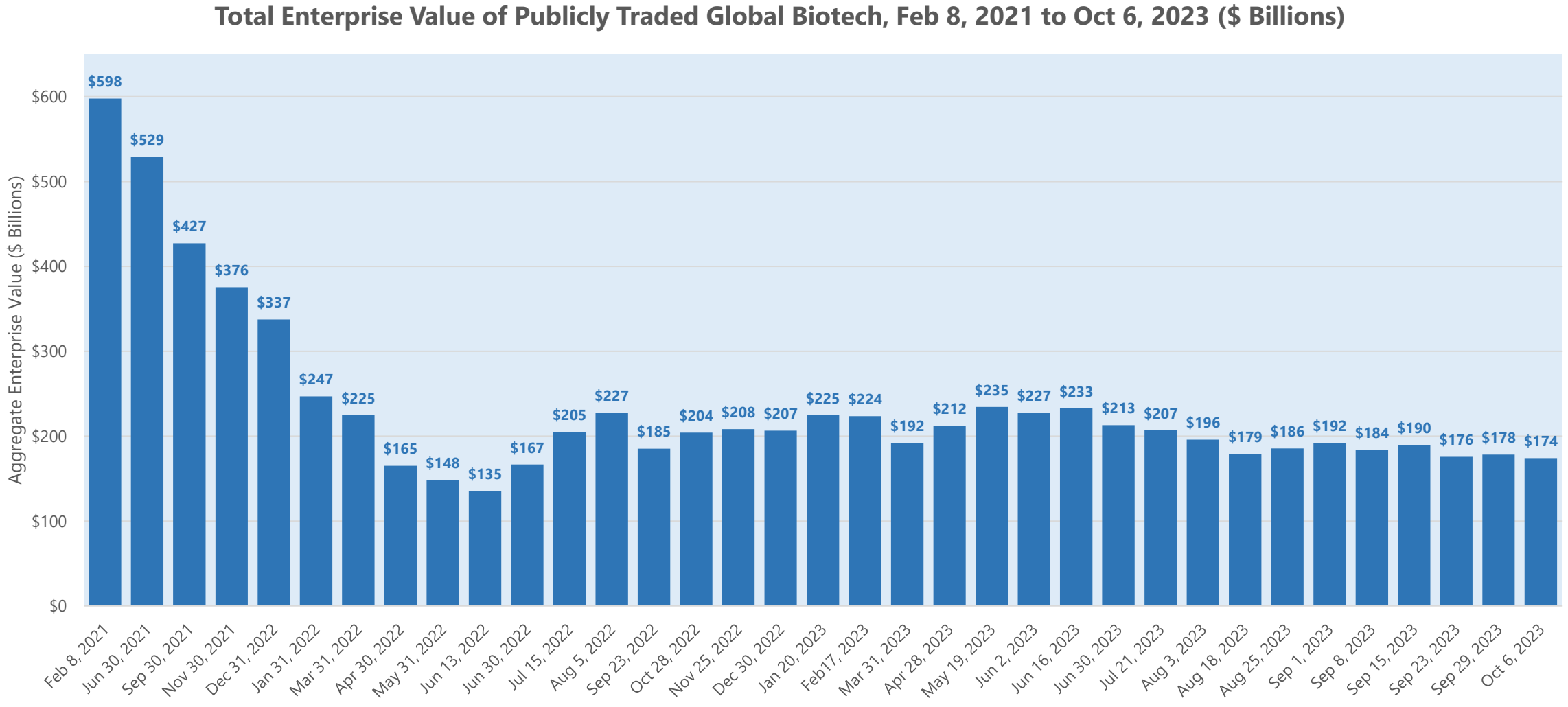



* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

# Total Global Biotech Sector Value Down 2.3% Last Week

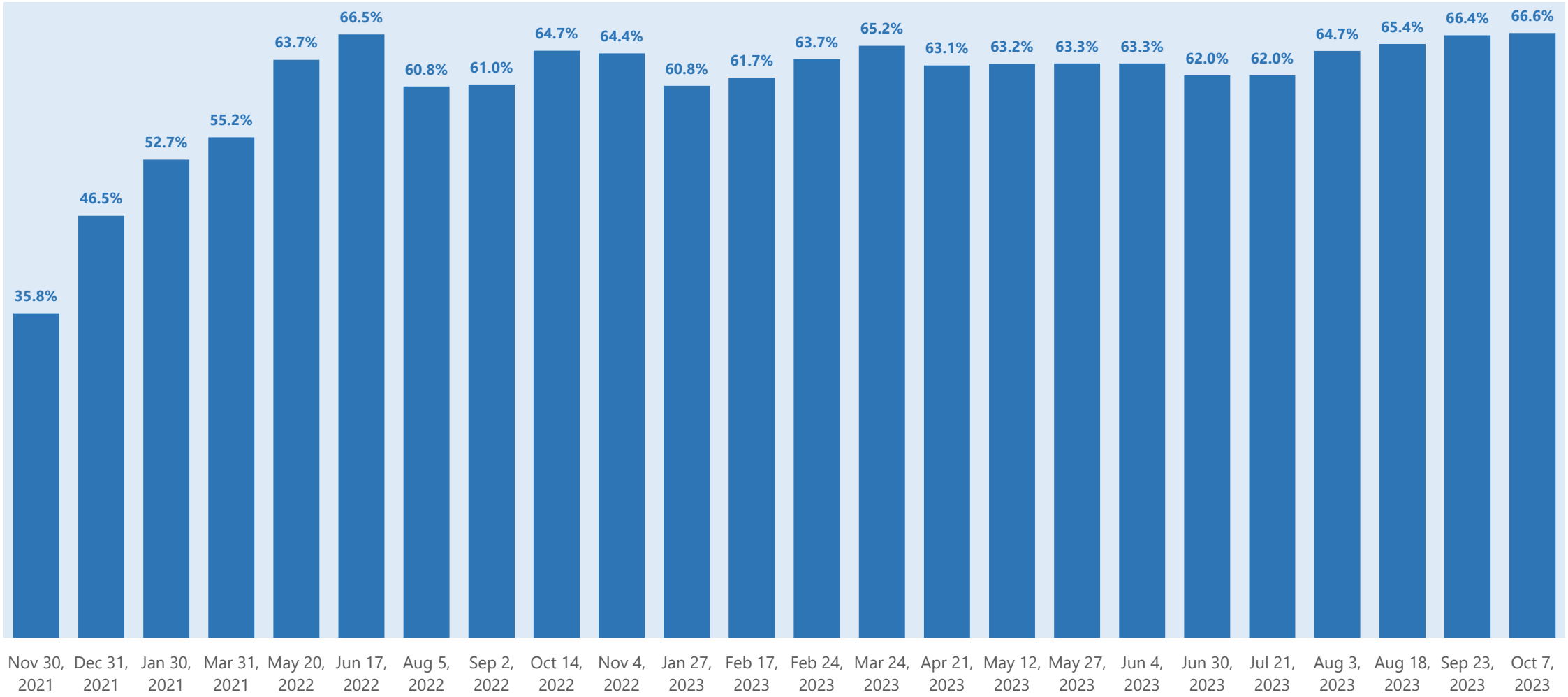
**The total value of the global biotech sector fell 2.3% last week (-$4 billion) amidst broad sector weakness. In total, 61% of stocks declined. The biggest value declines were at Immunovant (-$216mm), Repare (-$170mm) and Northwest Biotherapeutics (-$150mm).**




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

# Two Thirds of Biotechs Are Now Worth Less Than $100 Million

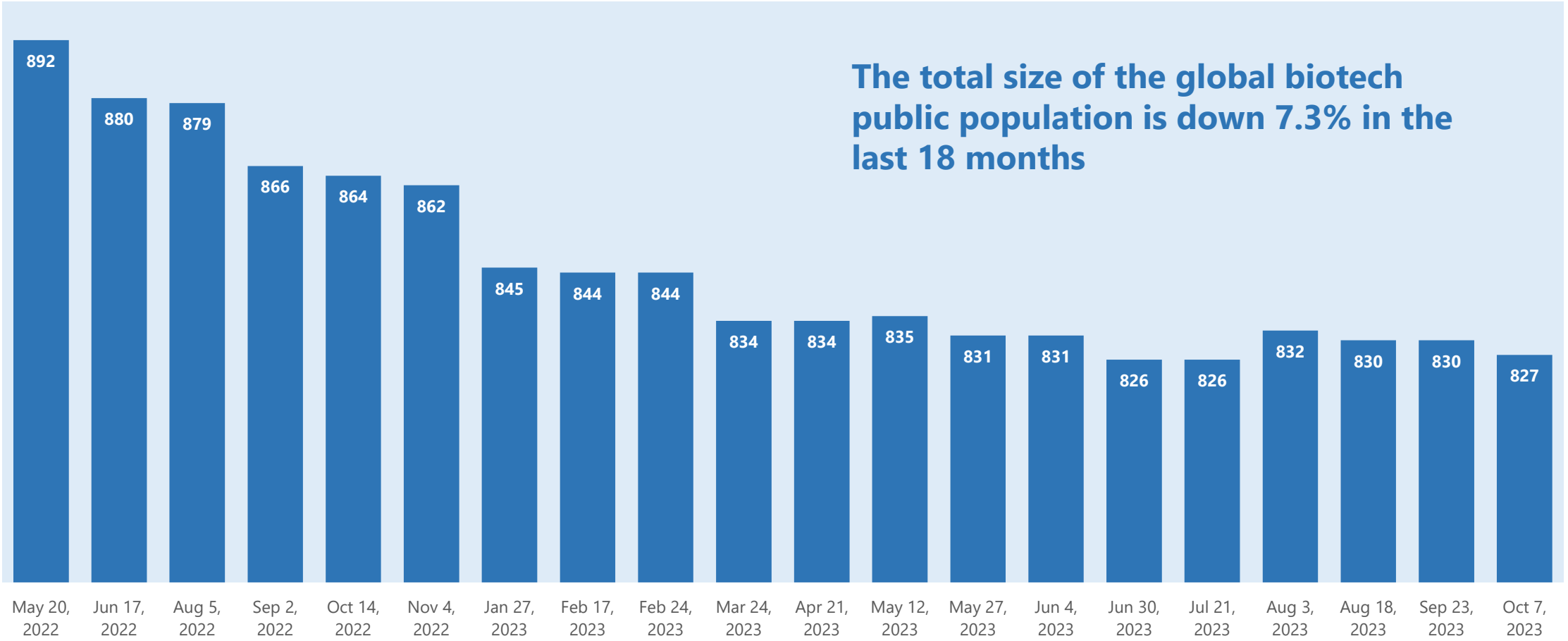
**Percent of Global Biotechs with an Enterprise Value Under $100mm, Nov 2021 to Oct 2023 (N=827)**




Source: CapitalIQ and Stifel Analysis

# Number of Remaining Public Biotechs

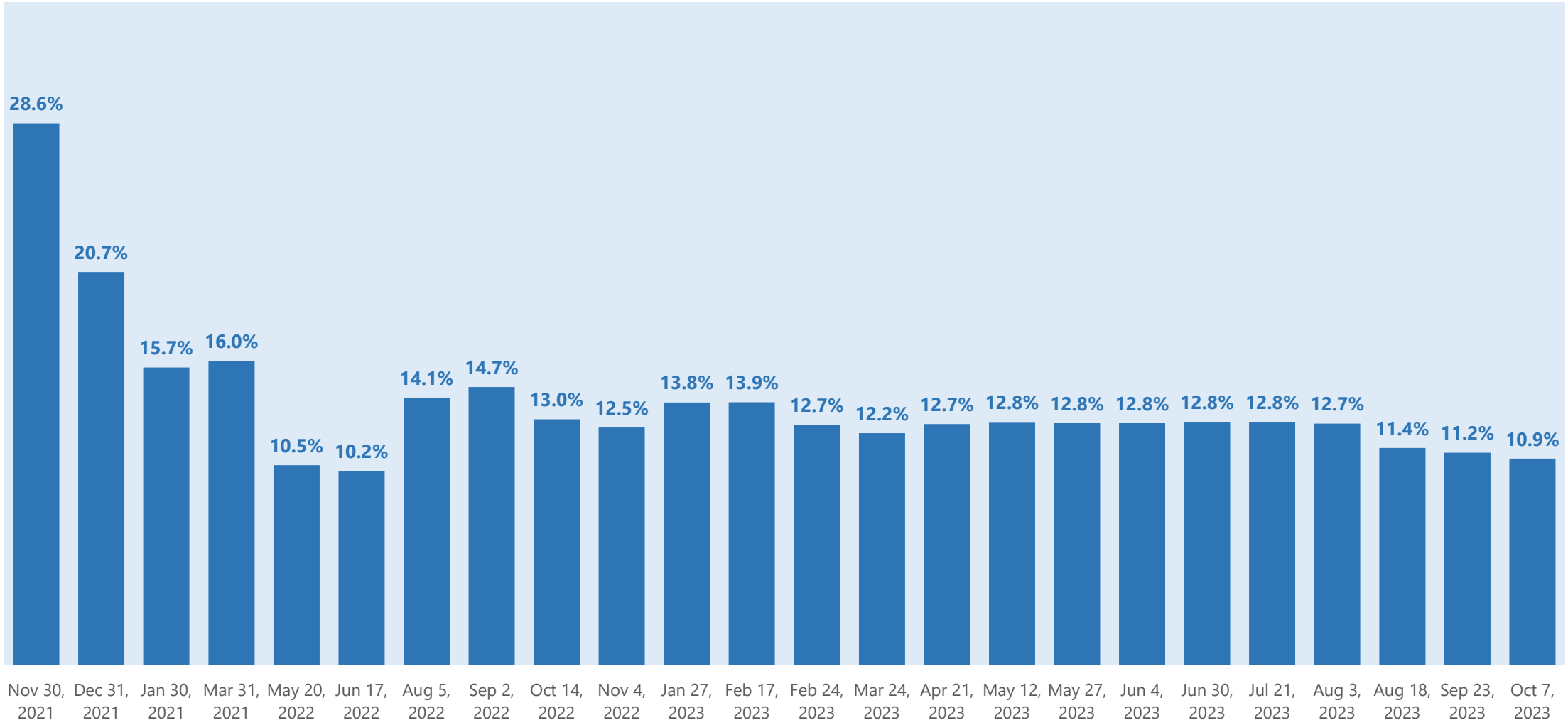
**Number of Publicly Traded Biotech Companies Worldwide, May 2022 to October 2023**




Source: CapitalIQ and Stifel Analysis

# Number of Companies Worth Over $500mm Shrinking

**Percent of Global Biotechs with an Enterprise Value of $500mm or More, Nov 2021 to Oct 2023**



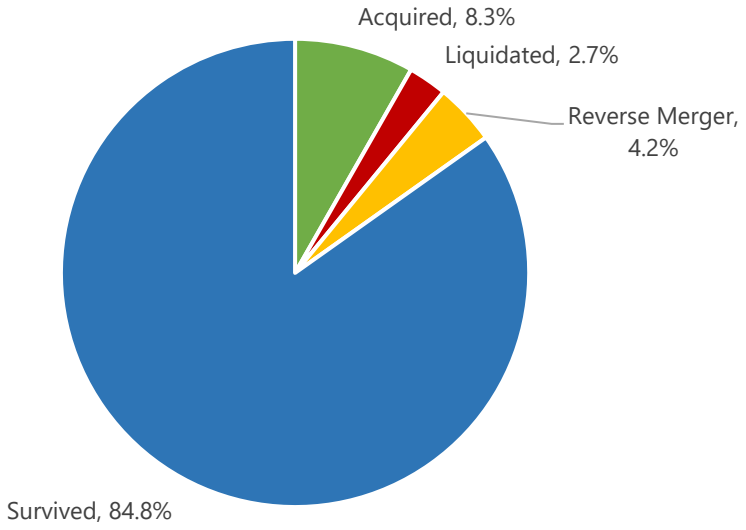

Source: CapitalIQ and Stifel Analysis

# Biotech Cohort Analysis (The Class of February 2021):
## Where are They Now and What Happened?

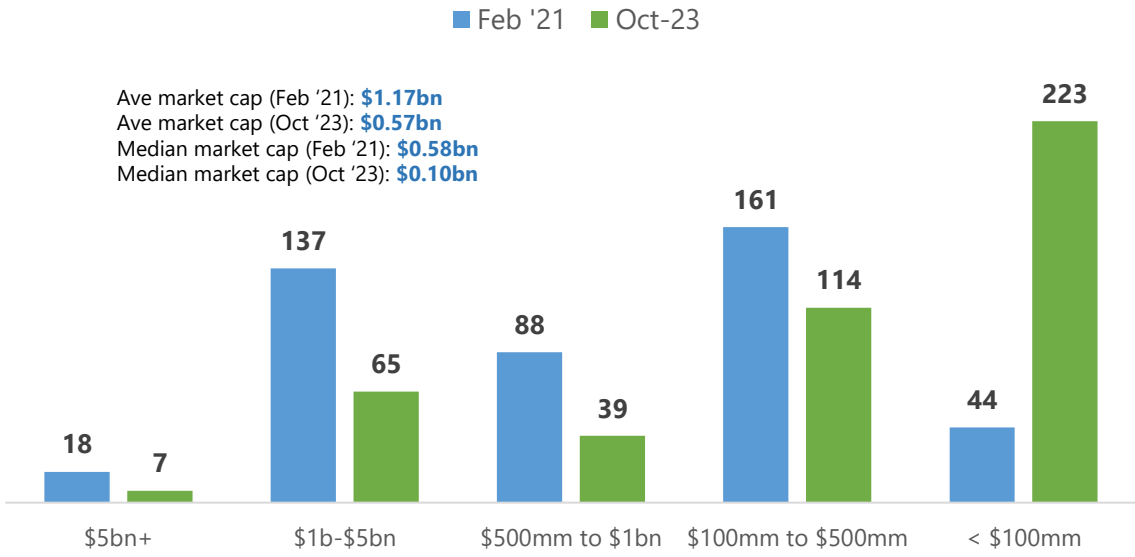
We looked at all 448 Nasdaq-listed biotech companies in our database as of Feb 21, 2021 (the peak of the market) and ask what happened to them since and how have they performed since. We are motivated by a number of analyses shared in recent weeks on Twitter saying that small caps have been disproportionately crushed in recent years. Because many companies in the cohort have disappeared, we tracked down the market cap at the time of exit to compare to the market cap as of Feb 21, 2021.

Roughly 85% of the companies in the cohort are still around today and 8% were bought while 7% were either liquidated or went through a reverse merger. The total market cap of the portfolio in Feb '21 was $527bn and today is $257bn (inclusive of M&A/liquidations). Of this, $194bn in market cap is associated with companies that are still public today.

**Fate of Nasdaq-Listed Public Biotechs on Feb 21, 2021 (last 32 months)**

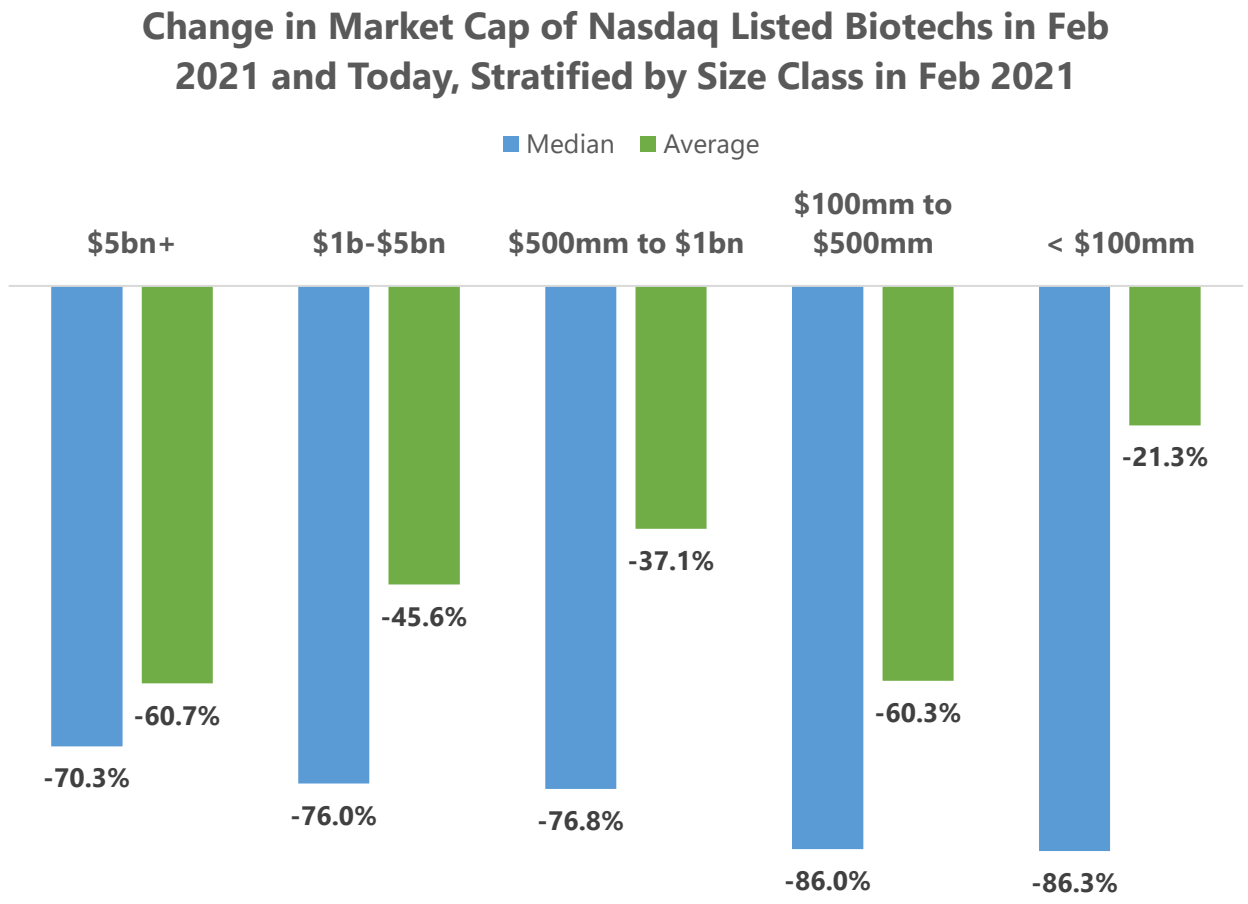



**The Nasdaq-Listed Biotech Population by Size Class in Feb 21 and Today**




Source: CapitalIQ and Stifel Analysis

# Biotech Cohort Analysis (The Class of February 2021):
## Change in Value from Then to Now




The median value change was lower for larger companies and the average value change was lower for smaller companies.

However, the *average value change* has been lower for the largest companies in the group (those that were over $5bn in value in Feb 2021).

The average change in value of biotechs that were worth $100mm or less in Feb 2021 is down 21.3% since then versus 60.7% for the $5bn+ companies at the time.

Ultimately, if one is an investor, the average effect is a lot more important than the median effect. For this reason, we would say that, if anything, it is small caps that have suffered least during the selloff.

The reason is somewhat obvious. These companies had less to lose.

Source: CapitalIQ and Stifel Analysis

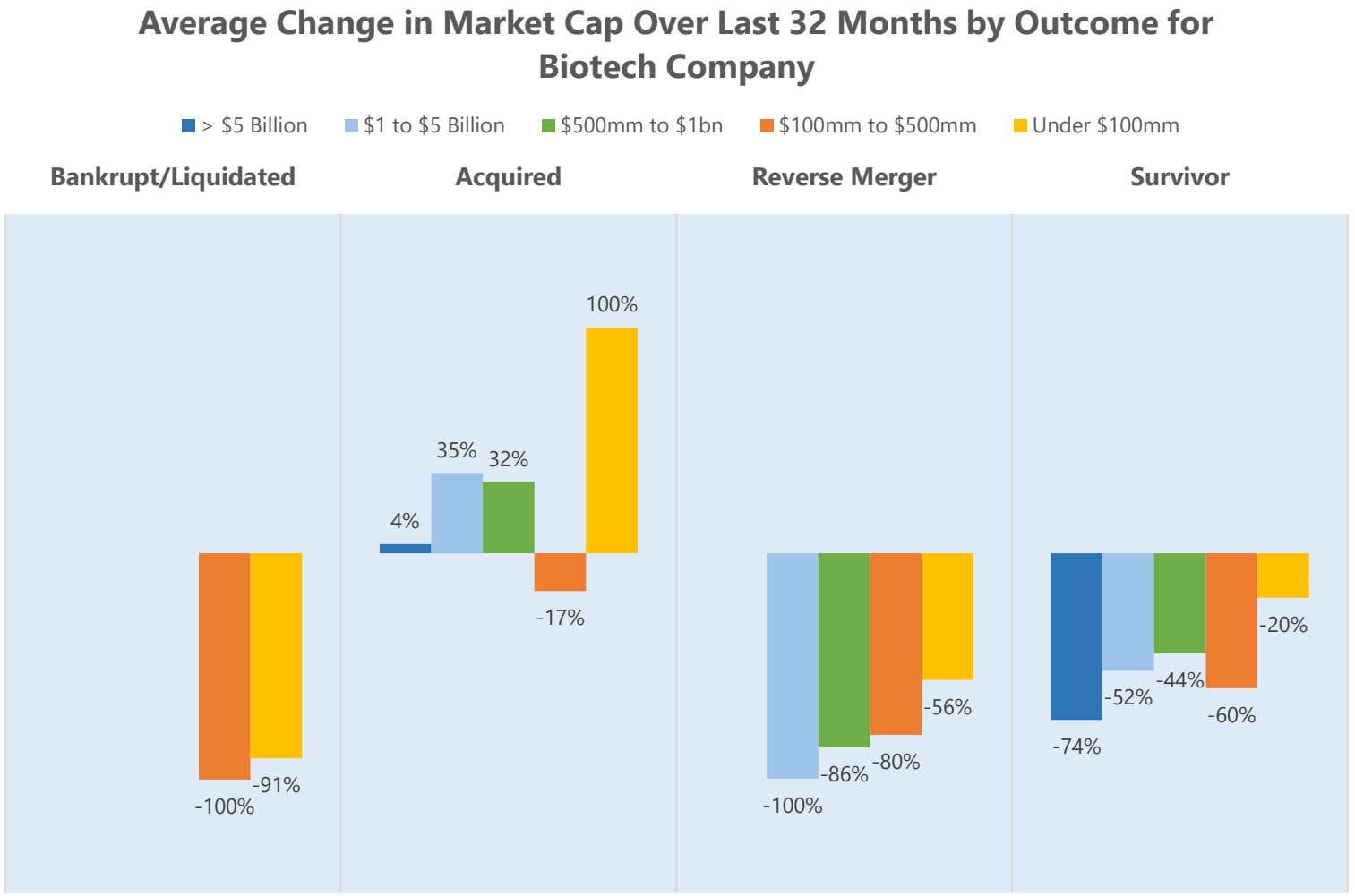
# Biotech Cohort Analysis (The Class of February 2021):
## Outcomes by Size Class

**The odds of survival were lowest for companies with market caps in Feb 2021 of less than $100mm. The highest odds of making it to now were for companies worth $1 billion to $5 billion in market cap in February 2021. The chances of being bought were highest for company's worth over $5 billion and lowest for those worth under $500 million in February 2021. Reverse mergers were disproportionately more likely for companies with market caps under $100mm in February 2021.**

| Market Cap Category (Feb 2021) | Number in Feb 2021 | Number in Oct 2023 | Percent Bought | Percent Liquidated | Percent Reversed | Percent Survived |
|---|---|---|---|---|---|---|
| Overall | 448 | 448 | 8.3% | 2.7% | 4.2% | 84.8% |
| $5bn+ | 18 | 7 | 16.7% | 0.0% | 0.0% | 83.3% |
| $1b-$5bn | 137 | 65 | 8.0% | 0.0% | 1.5% | 90.5% |
| $500mm to $1bn | 88 | 39 | 11.4% | 0.0% | 3.4% | 85.2% |
| $100mm to $500mm | 161 | 114 | 6.2% | 6.2% | 3.7% | 83.9% |
| < $100mm | 44 | 223 | 6.8% | 4.5% | 18.2% | 70.5% |

Source: CapitalIQ and Stifel Analysis

# Biotech Cohort Analysis (The Class of February 2021):
## Value Changes by Company Fate




This analysis shows the average change in value from Feb 22, 2021 to October 6, 2023 by the fate of companies.

Bankruptcy, liquidation and reverse merger, not surprisingly, were associated with the biggest drops in value. Interestingly, smaller companies doing reverses seem to have dropped less.

Among acquired companies those that were worth $5bn or more did not yield much additional return for holders while those that were $500mm to $5bn and under $100mm still had significant return to provide.

Source: CapitalIQ and Stifel Analysis

# List of Nasdaq-Listed Biotech Companies That Did Not Survive From Feb 2021 to Oct 2023

## Acquired

Acceleron Pharma
Akouos
Albireo Pharma
AGTC
AVEO Pharmaceuticals
Ayala Pharmaceuticals
Checkmate Pharmaceuticals
ChemoCentryx
Chinook Tx
Concert Pharma
Constellation Pharmaceuticals
Decibel Therapeutics
Dicerna Pharmaceuticals
Entasis Therapeutics
Five Prime
Forma Therapeutics
F-star Therapeutics
IVERIC bio
Jounce Therapeutics
Kadmon Holdings
LogicBio Therapeutics
Mirati Therapeutics
Myovant Sciences
NantKwest
Opiant Pharmaceuticals
Orchard Therapeutics
Oyster Point Pharma
Pandion Therapeutics
Provention Bio
Reata Pharmaceuticals
Satsuma Pharmaceuticals
Sigilon Therapeutics
Spectrum Pharmaceuticals
Surface Oncology
TCR2 Therapeutics
Translate Bio
Turning Point Therapeutics
Urovant Sciences
Viela Bio

## Reverse Merger

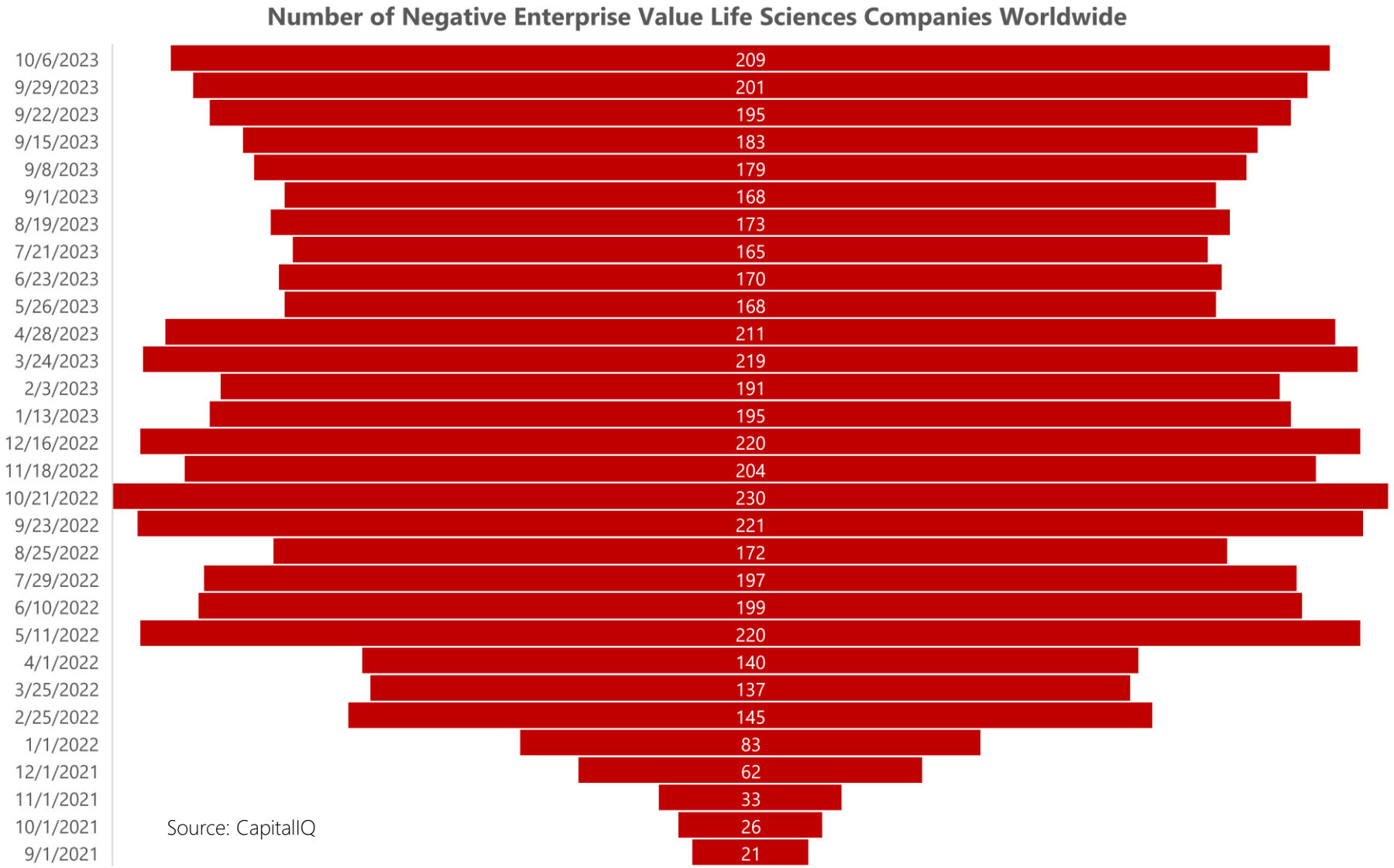
Aerpio Pharmaceuticals
Angion Biomedica
Brickell Biotech
Cancer Genetics
Catabasis Pharmaceuticals
Celsion Corporation
Cleveland BioLabs
Cortexyme
EyeGate Pharmaceuticals
Frequency Tx
Gemini Therapeutics
Graybug Vision
Idera Pharma
IMARA Inc.
Magenta Therapeutics
Neoleukin
Sesen Bio
Silverback Therapeutics
Sunesis Pharmaceuticals
Talaris Therapeutics
Tyme Technologies
Vallon Pharma

## Liquidation / Bankruptcy

9 Meters Biopharma
Aptinyx
Codiak BioSciences
Exicure
Fresh Tracks Therapeutics
Genocea
Histogen
Infinity Pharmaceuticals
Kaleido Biosciences
Metacrine
Novan
Otonomy
PhaseBio Pharmaceuticals
PLx Pharma
PolarityTE
Rubius
SIO Gene Therapies
Tricida

Source: CapitalIQ and Stifel Analysis

# Number of Negative Enterprise Value Life Sciences Companies Rose to 209 in Last Week




Source: CapitalIQ

**The count of negative EV life sciences companies worldwide rose from 201 a week ago to 209 last Friday.**

**This count is a measure of overall sector distress.**

**Obviously, after a respite in June and July, financial conditions in the life sciences sector are becoming more challenging.**

# Public Life Sciences Sector Value Fell Last Week

**The total enterprise value of the publicly traded life sciences sector fell by 0.6% last week ($53 billion). The sectors that dropped the most were OTC, life science tools and biotech. Commercial pharma was up due a jump in Lilly value. Lilly's $25 billion rise last week exceeded the enterprise value of Alnylam.**

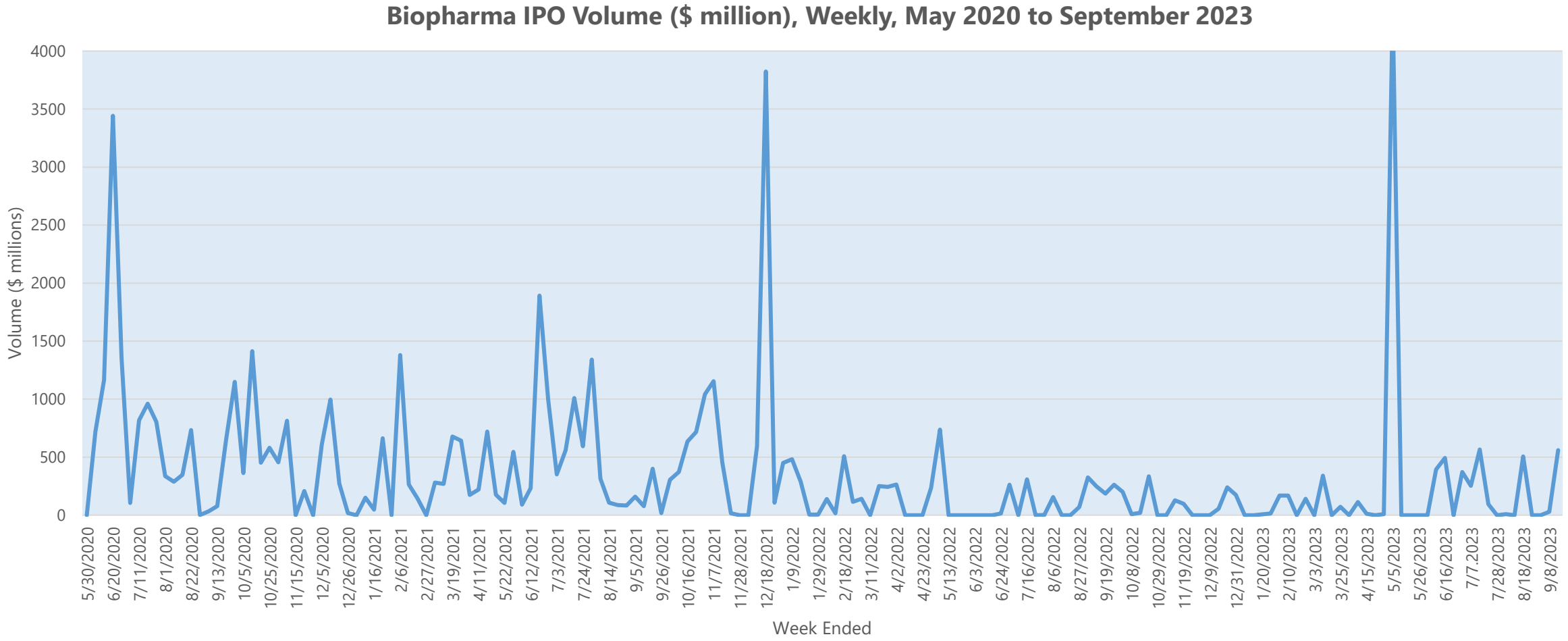
| Sector | Firm Count | Enterprise Value (Oct 7, 2023, $millions) | Change in Last Week (percent) | Change in Last Month (percent) | Change in Last Year (percent) |
|---|---|---|---|---|---|
| API | 81 | $80,722 | -0.6% | 3.3% | -0.8% |
| Biotech | 815 | $172,752 | -4.0% | -6.8% | -5.1% |
| CDMO | 40 | $158,709 | 1.3% | -3.9% | -7.7% |
| Diagnostics | 83 | $227,926 | -2.6% | -7.4% | 3.6% |
| OTC | 31 | $28,328 | -4.3% | -5.2% | 0.6% |
| Commercial Pharma | 724 | $5,756,642 | 0.1% | -1.6% | 11.2% |
| Pharma Services | 40 | $199,424 | -0.2% | -1.9% | 12.4% |
| Tools | 53 | $641,780 | -4.2% | -8.1% | -11.7% |
| Devices | 181 | $1,497,726 | -1.0% | -5.2% | 3.0% |
| HCIT | 11 | $22,661 | -0.8% | -2.6% | -4.3% |
| **Total** | **2059** | **$8,786,670** | **-0.6%** | **-3.0%** | **6.7%** |

Source: CapitalIQ

# Capital Markets Environment

# IPO Market Quiet

**The IPO market has remained quiet as the macro situation has dominated the market in recent weeks. Last week saw the Novartis / Sandoz spin get completed.**




Source: Data from CapitalIQ and Stifel research.

# In Splitting from Novartis, Sandoz Makes Muted Market Debut

**Zoey Becker, *Fierce Pharma*, Oct 4, 2023 (excerpt)**

After more than a year of preparation, Sandoz has officially parted ways with Swiss drug giant Novartis. But the company's day-one valuation lagged what some analysts had projected.

The drugmaker debuted on the SIX Swiss Exchange at a valuation of 10.3 billion Swiss francs ($11.2 billion), according to Reuters. Analysts had previously published expected ranges of $11 billion to $26 billion for the company, the news service reports.

Still, the spinoff comes as stock indices around the world have been in retreat in recent weeks.

Sandoz debuts as a generic and biosimilar powerhouse. The company believes the industry is positioned to grow “steadily” over the next decade because of “underlying demand," the company said in a press release.

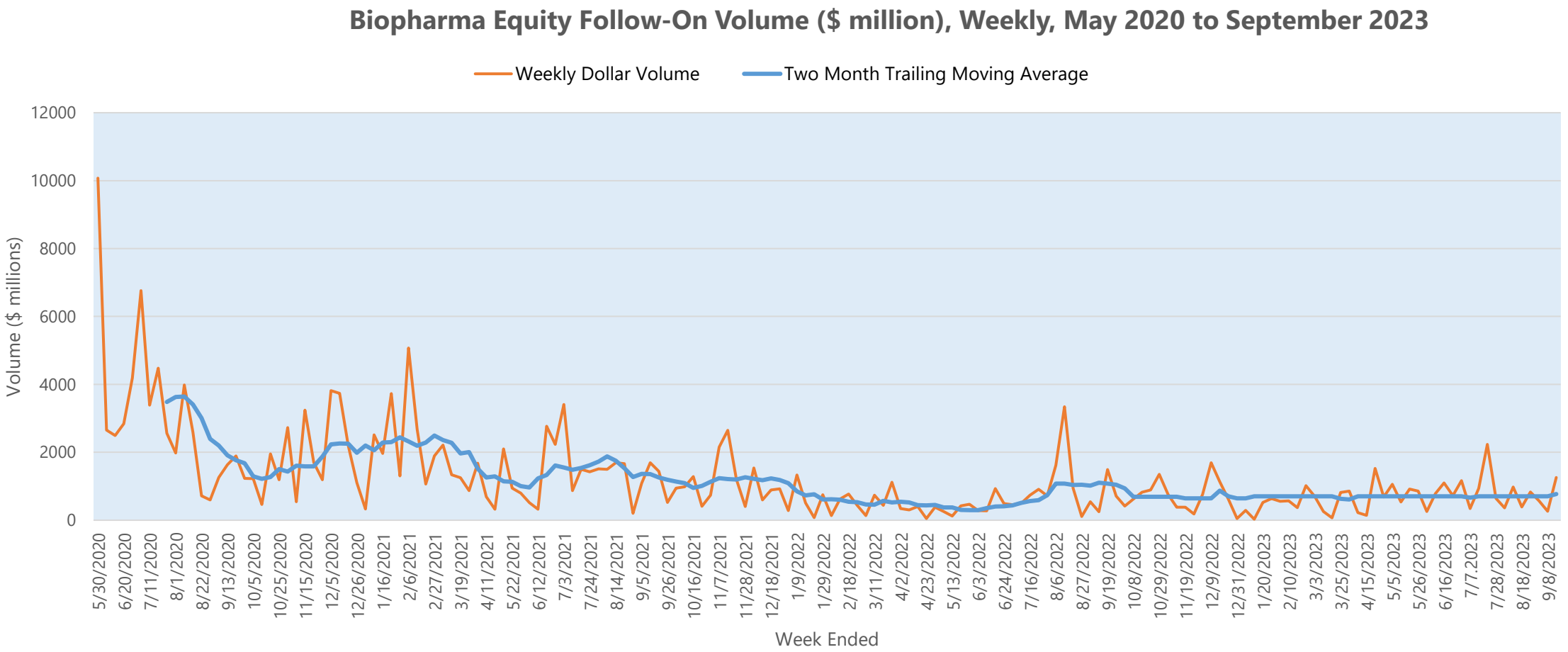
When Novartis announced the official separation date of Oct. 4, it proposed a stock distribution scheme, offering shareholders one Sandoz share for every five Novartis shares they own.

SANDOZ

Source: https://www.fiercepharma.com/pharma/sandoz-officially-splits-novartis-its-swiss-stock-exchange-debut

# Last Week Saw $630mm in Follow-On Equity Offerings

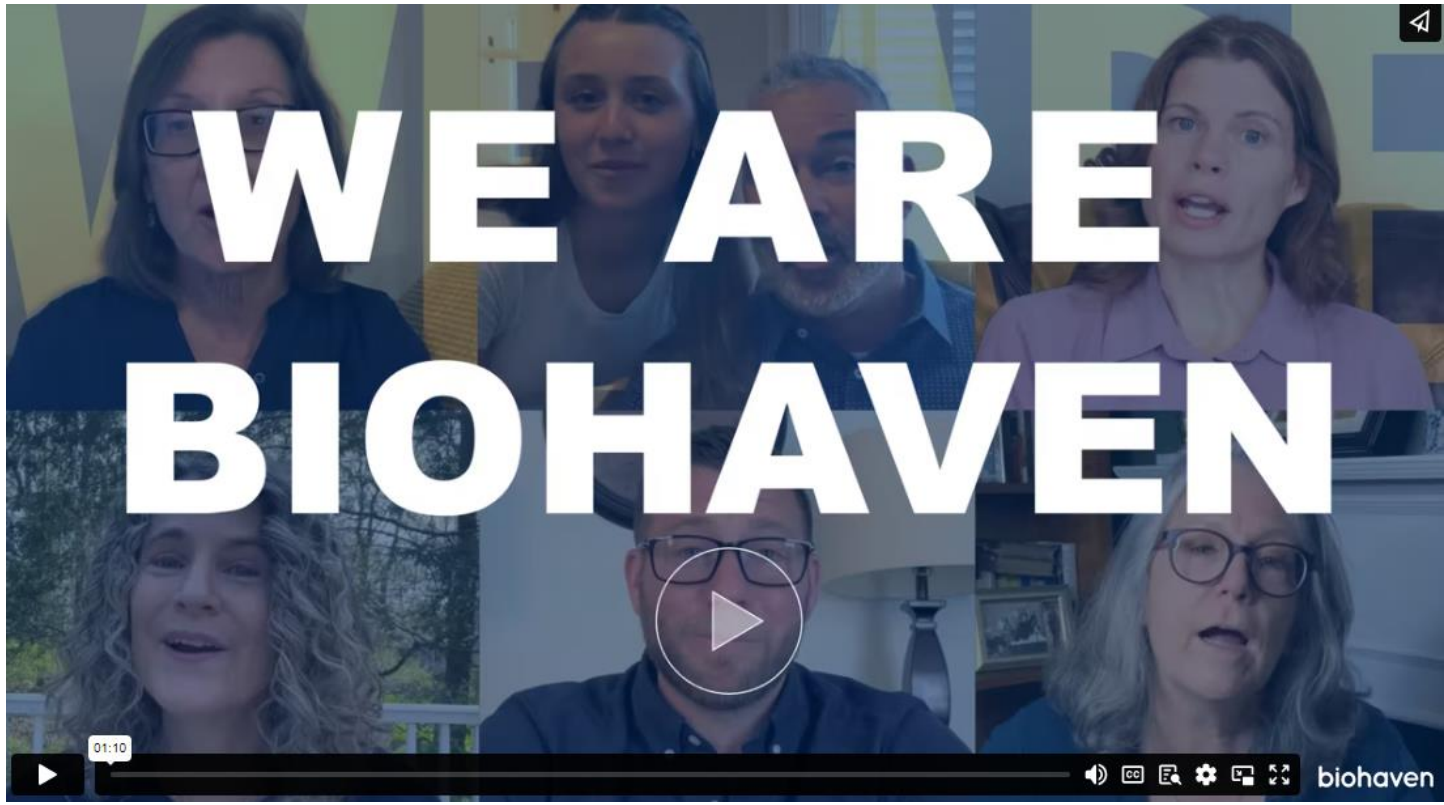
**With a backdrop of market volatility, the follow-on market was relatively muted last week. Biohaven raised $258 million on the back of promising data for its IgG degrader. SAB Biotherapeutics completed a $130 million PIPE.**




Source: Data from CapitalIQ and Stifel research.

# Biohaven Raises $259 Million in Follow-On Offering

**NEW HAVEN, Conn., Oct. 5, 2023 /PRNewswire/**-- Biohaven Ltd. (NYSE: BHVN), a global clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of life-changing therapies to treat a broad range of rare and common diseases, today announced the closing of its underwritten public offering of 11,761,363 of its common shares, which includes the full exercise of the underwriters' option to purchase 1,534,090 additional common shares, at a public offering price of $22.00 per share. The gross proceeds from the offering were approximately $258.7 million before deducting underwriting discounts and commissions and offering expenses payable by Biohaven. Biohaven intends to use the net proceeds received from the offering for general corporate purposes.




Source: https://ir.biohaven.com/news-releases/news-release-details/biohaven-announces-closing-public-offering-and-full-exercise-0

# SAB Biotherapeutics Announces Private Placement of up to $130 Million to Develop Lead Drug Candidate for Type 1 Diabetes

**SIOUX FALLS, S.D., Oct. 02, 2023 (GLOBE NEWSWIRE)** -- SAB Biotherapeutics (Nasdaq: SABS), a clinical-stage biopharmaceutical company with a novel immunotherapy platform that is developing fully-human anti-thymocyte immunoglobulin (hIgG) for delaying the onset or progression of type 1 diabetes (T1D), today announced the Company has entered into a securities purchase agreement (the "Securities Purchase Agreement") with certain accredited investors (the "Investors"), pursuant to which the Company agreed to issue and sell shares of preferred stock in a private placement (the "Offering"). The Offering will provide up to $130 million in gross proceeds to SAB, which will be used to fund the company's lead research program, SAB-142, a potential disease-modifying treatment for T1D. The full proceeds, when funded, are expected to fund the company through 2026 and topline Phase II results.

The transaction is being led by RA Capital Management, with participation from BVF Partners, Sessa Capital, Commodore Capital, RTW Investments, Marshall Wace, and the JDRF T1D Fund.

SAB will use the funds to clinically advance SAB-142, its lead therapeutic candidate for T1D, which is expected to advance to clinical trials in Q4 2023. SAB-142 is a fully-human alternative to rabbit anti-thymocyte globulin (rATG). SAB-142's mechanism of action is similar to that of rATG, which has been clinically validated in multiple clinical trials for T1D, demonstrating the ability to slow down disease progression in patients with new or recent onset of Stage 3 T1D.

"We're pleased to have the support of this world-class syndicate of investors in the field of type 1 diabetes," said Eddie Sullivan, co-founder, President, and Chief Executive Officer of SAB. "This financing will enable us to advance SAB-142, our disease-modifying immune therapy with the potential for annual redosing to halt diabetes progression, into human trials in the coming months. Our mission is to help shift the T1D treatment paradigm from daily maintenance with devices and exogenous insulin to a disease-modifying approach that offers durable preservation of pancreatic function by addressing the root cause of T1D."

Two clinical trials have shown that a single, low dose of rATG has demonstrated the ability to modulate the body's immune response to help slow beta cell destruction and preserve the ability of these cells to generate insulin, which the body needs to regulate blood sugar and carry out all human activities. SAB-142, like rATG, directly targets multiple immune cells involved in destroying pancreatic beta cells. By stopping immune cells from attacking beta cells, this treatment preserves insulin-producing beta cells. However, most humans treated with rATG develop serum sickness and anti-drug antibodies from exposure to the rabbit-derived antibody. SAB-142 is a human antibody, intended to allow safe, consistent re-dosing for T1D, a lifelong chronic disease, without the potential risk of inducing the major adverse immune reactions that can occur with administration of a fully animal ATG.

Source: https://ir.sab.bio/news-releases/news-release-details/sab-biotherapeutics-announces-private-placement-130-million

# PIPEs in Biotech Fundraising: Is This Growing Trend Fueled by Economic Uncertainty Here to Stay?

## Roohi Mariam Peter, *Labiotech*, October 2, 2023 (excerpt)

"A private investment in public equity or PIPE is an investment made by private accredited investors in public stock at a discounted rate. This stock is not freely tradable, and because it's privately held, it will be restricted for a period of time. This kind of investment was thought to be less popular, but now that's a thing of the past. Currently, with capital drying up, biopharmaceutical companies have hit a rough patch. And so, many are willing to venture out and explore non-typical ways to raise money.

"The biopharma sector and small-cap sectors have faced economic headwinds over the last few years," said Warren Duncan, chief financial officer (CFO) at Filament Health. "Although potentially more dilutive than sources of capital that were previously available to biopharma companies, it is encouraging to see capital being invested in the biopharma sector."

### Can PIPEs help counter the biotech financing crisis?

So, it's no surprise that young biotechs that have gone public are looking for new ways to obtain funds. Earlier this year, American clinical-stage company Taysha Gene Therapies, raised $150 million through a PIPE funding led by RA Capital Management, PBM Capital and RTW Investments, among others. However, last week, as Taysha pulled the plug on its lead gene therapy candidate for the treatment of a rare central nervous system (CNS) disorder, following a U.S. Food and Drug Administration (FDA) meeting, it now expects its cash runway to last into the fourth quarter of 2025.

Over the year, other major PIPE financings have taken place, including a $160 million deal for American gene therapy company Krystal Biotech, U.K.-based mental healthcare pharmaceutical COMPASS Pathways bagging $125 million financing upfront with up to an additional $160 million tied to exercise of warrants, and Canadian precision medicine company ProMIS Neurosciences securing $20.4 million. And, only last month, American clinical-stage biotech Inhibrx announced that it would receive $200 million in financing that was limited to some of the company's existing investors.

With the IPO window shut and capital being scarce, companies do not have a lot of bargaining power with investors, according to Tim Opler of Stifel.

"PIPE investments have become quite popular," said Opler. "I would say one week in three these days, the PIPE market's actually bigger than the follow on market. And so, the PIPE market has become quite important. And if you went back two or three years, you would not see that at all."

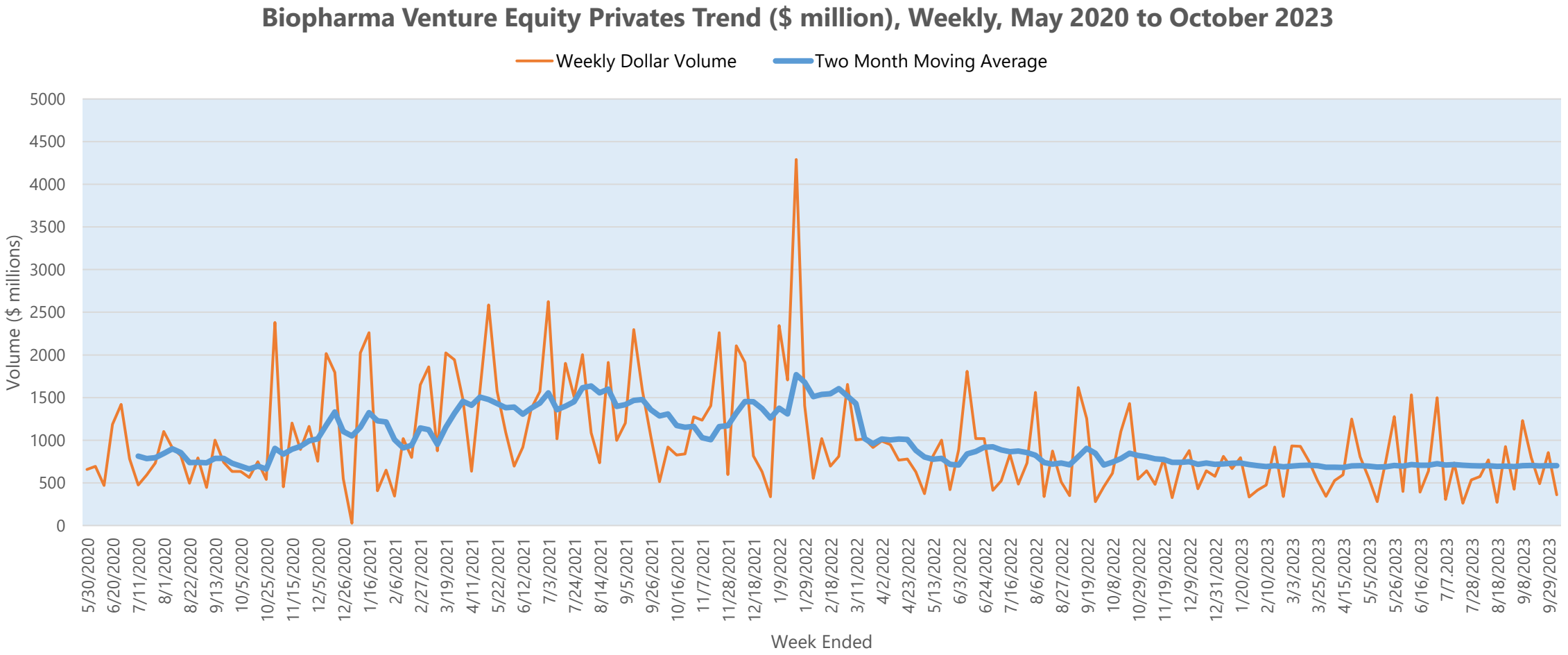
As this is a "time of life and death for biotech," Opler explained that in the next two years, many biotechs will have gone out of business.

"If you can raise money in a PIPE, that can make a huge difference in whether or not your company survives," he said. "The good news is that PIPEs are there… We're in a very, very difficult time for the market. And so, the availability of the PIPE market is obviously, overall, a good thing" said Tim Opler."

Source: https://www.labiotech.eu/in-depth/pipe-financing-biotech/

# Venture Equity Market Quiet Last Week

**Last week saw 19 biopharma companies raise $360 million in the venture equity market. The largest deal to announce was a $100mm raise by Iambic Therapeutics, a San Diego AI focused drug discovery company.**




Source: Data from CapitalIQ, Crunchbase.

# Iambic Therapeutics Announces Close of $100 Million Series B Financing to Advance AI-Discovered Therapeutics

**SAN DIEGO—October 3, 2023--(BUSINESS WIRE)** -- Iambic Therapeutics (formerly known as Entos), a biotechnology company developing novel therapeutics from its unique generative AI discovery platform, today announced the closing of an oversubscribed $100 million Series B financing co-led by Ascenta Capital and Abingworth, and also including new investors NVIDIA, Illumina Ventures, Gradiant Corporation, and independent board member Bill Rastetter. Existing investors also participated, including Nexus Ventures, Catalio Capital Management, Coatue, FreeFlow, OrbiMed, and Sequoia Capital. As part of the Series B, Iambic is delighted to welcome two new board members, Evan Rachlin, M.D., from Ascenta Capital and Kurt von Emster from Abingworth.

"We were struck by the originality of these molecules, offering distinctive approaches in both deeply validated and more novel biological pathways," added Evan Rachlin, M.D., Co-founder and Managing Partner of Ascenta Capital. "Iambic's platform enables a more creative and expansive exploration of how to treat diseases with profound unmet needs. We are delighted to partner with Tom and his extraordinary team in translating these thoroughly tested medicines into humans."

"Abingworth is proud to support the remarkably talented team at Iambic in its drive to revolutionize drug discovery and speed to the market with highly selective drugs," said Kurt von Emster, Managing Partner and Head of Life Sciences at Abingworth.

"AI-driven technologies, including methods that Iambic and NVIDIA researchers have built together, are charting a new path for researchers in the discovery of new therapeutic candidates," said Rory Kelleher, Director of Healthcare and Life Sciences at NVIDIA. "NVIDIA-accelerated computing and software are helping industry pioneers like Iambic drive scientific breakthroughs and our continued collaboration aims to speed innovation in drug discovery."

"At Iambic, our world-class team has combined physics and AI to create a differentiated drug discovery platform that achieves a step-change in the speed and success rate for delivering best-in-class and first-in-class development candidates to clinic. With the Series B funding, we intend to advance multiple AI-discovered candidates into the clinic and expand our pipeline, demonstrating how the Iambic platform can deliver better therapeutics to patients in less time, with optimized target product profiles for greater likelihood of clinical success."

**Tom Miller**
Founder and Chief Executive Officer

Source: https://www.businesswire.com/news/home/20231003865353/en/Iambic-Therapeutics-Announces-Close-of-Oversubscribed-100-Million-Series-B-Financing-to-Advance-AI-Discovered-Therapeutics-into-Clinical-Development-and-Enters-Collaboration-with-NVIDIA

# Novo Holdings Benefiting from Semaglutide Success

**James Waldron, *Fierce Biotech*, October 6, 2023 (excerpt)**

"But while semaglutide revenues could bring "a hell of a lot of money" his team's way in the coming years, he downplayed the suggestion that this would significantly alter Novo Holdings' biotech investment strategy. "We've developed our teams in a way that we are very responsible in how we deploy that capital, and I feel the responsibility more than ever," Kutay says.

One way we may see Novo Nordisk's commercial success filter down is in the continued expansion of Novo Holdings' geographic footprint. In recent years, the fund manager has opened offices in the U.S. biotech hubs of Boston and San Francisco as well as London, Singapore and Shanghai.

Novo Holdings currently employs around 160 employees, with that number set to rise to around 180 by year-end. "I think there'll be a little bit more growth after that," he adds. "But … I think once we get to 180, that gives us a lot of scope."

Novo Holdings has already been involved in a number of biotech megarounds this year, including Amolyt Pharma's $138 million series C, which the French company is using to push its hypoparathyroidism drug through phase 3 trials, and Switzerland's Alentis Therapeutics, which completed a $105 million series C to fund trials of its anti-Claudin-1 antibodies for tumors and organ fibrosis.

Despite being run at arm's length from Novo Nordisk, the fund manager does try to "avoid playing in the same sandpit" as the Big Pharma by steering clear of disease areas like diabetes or obesity, Kutay explains.

"If we're uncertain, we just pick up the phone and say, 'Look, does this conflict with what you're doing in any way?'" he says. "If the answer is no, then we proceed."

Yet, while Novo Holdings has Novo Nordisk's profits to play with, Kutay explains that the way his team picks potential biotech investments is not influenced by Novo Nordisk's overarching strategy.

"We are a 100% returns-driven investor," he says. "There is no strategic component to what we do. We feel very proud that the more money we generate, then the more good the foundation can do.""

Source: https://www.fiercebiotech.com/biotech/flush-wegovy-cash-novo-nordisks-owner-widens-investment-strategy-beyond-biotech

# Hedge Funds Sharply Curtail Private Investments

**Stephen Taub, *Institutional Investor*, October 4, 2023 (excerpt)**

Tiger Global Management has all but disappeared from the private markets. The Tiger Cub, co-headed by Chase Coleman and Scott Shleifer, made just six new investments in start-ups in the third quarter, according to Crunchbase. Altogether, the firm has made only 27 new investments over the first three quarters of the year.

This is still far more than any other alternatives firm that is also known for its hedge funds. But investors may be surprised, given Tiger Global once did a deal a day, including on weekends. Still, that was in 2021 and the first half of 2022, an entirely different era for venture capital.

Since then, many technology valuations have plummeted. In addition, the IPO market is still struggling and the SPAC (special purpose acquisition company) market has collapsed, making it much harder for fledgling companies to go public.

The erosion of those markets in turn made it difficult for asset managers to cash out or at least partially monetize and establish a valuation for their private investments. It has also become tougher for venture capital firms to raise money in the past couple of years.

According to CB Insights, global venture funding dropped in the second quarter to its lowest level since second-quarter 2020 and U.S. venture funding fell 27 percent, to $31.3 billion from the first quarter of 2023.

Tiger Global is not the only hedge fund firm with a previously robust VC operation to continue to sharply curtail private investing in the third quarter. Many other well-known firms that similarly emphasize tech, internet, consumer, and other new-economy companies have also been much less active.

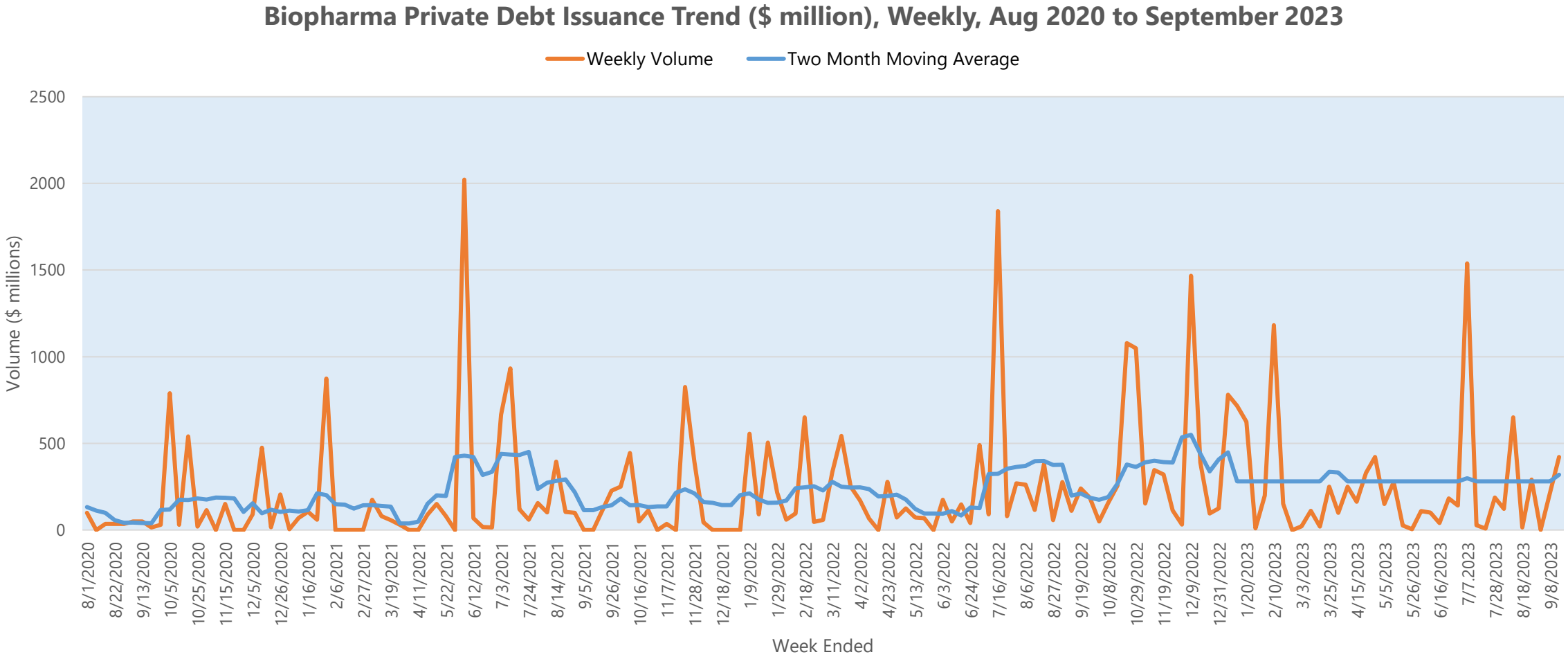
For example, Coatue Management completed just ten deals in the latest three-month period, according to Crunchbase. This is more than in each of the two previous quarters. It has made 25 new private investments in total this year, just two fewer than Tiger Global. By comparison, Coatue made 31 VC investments in first-quarter 2022 and 165 in 2021, according to the database.

Several other prominent hedge fund firms, however, made no new private investments for at least the third straight quarter and in several cases for more than a year.

Source: https://www.institutionalinvestor.com/article/2c9xxug1rt7op1nxach6o

# Weekly Global Biopharma Venture Debt Placements

**We saw four deals in the private debt market last week with $463 mm raised. The largest deal was a $430 million debt and equity investment by Blackstone into Amicus Therapeutics.**




Source: Data from CapitalIQ, Crunchbase.

# Amicus Therapeutics and Blackstone Enter into $430 Million Strategic Financing Collaboration

**PRINCETON, N.J., Oct. 02, 2023 (GLOBE NEWSWIRE)** -- Amicus Therapeutics (Nasdaq: FOLD), a global, patient-dedicated biotechnology company focused on discovering, developing, and delivering novel medicines for rare diseases, today announced that it has entered into a definitive agreement for a $430 million financing collaboration with funds managed by Blackstone (NYSE: BX). As part of the collaboration, Blackstone Life Sciences and Blackstone Credit have agreed to provide Amicus with a $400 million senior secured term loan facilitating a refinancing of existing debt and a $30 million strategic investment in Amicus's common stock. The financing collaboration allows Amicus to grow revenues and move toward profitability while delivering on its mission for patients and its vision of being one of the leading biotechnology companies focused on rare diseases.

Bradley Campbell, President and Chief Executive Officer of Amicus Therapeutics, stated: "This new financing with Blackstone strengthens our balance sheet and financial profile by reducing the interest rate versus our current debt, pushing out the amortization schedule and extending the amortization period. This strategic investment demonstrates Blackstone's commitment to Amicus' future and belief in the strong growth potential of Galafold and Pombiliti™ + Opfolda™ as we continue on our mission to develop medicines for people living with rare diseases."

Key features of this transaction include:

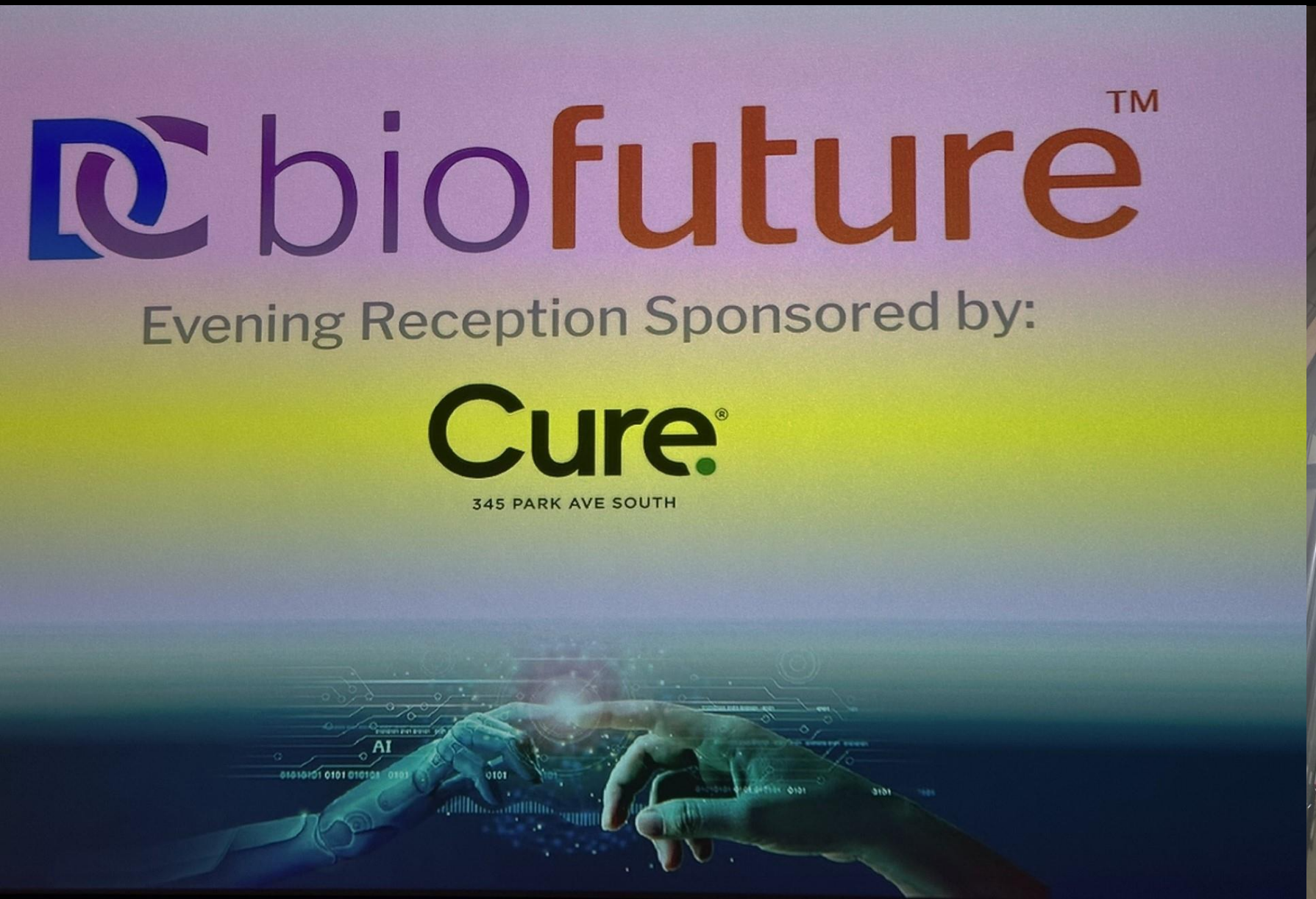
- $400M senior secured term loan facility; interest rate at adjusted Term SOFR plus 6.25%, subject to a 2.50% floor on Term SOFR
- $30M investment in Amicus common stock
- Requires interest-only payments until late 2026 and matures in October 2029
- The full amount of the loan and equity purchase will be available and fully drawn at the initial funding
- The proceeds will be used to refinance Amicus's existing debt and fund ongoing operations

Commenting on the arrangement, Craig Shepherd, Senior Managing Director with Blackstone Life Sciences and Brad Colman, Senior Managing Director with Blackstone Credit said: "Blackstone aims to provide customized financing solutions for the world's leading biotech and pharma companies across therapeutic areas to support mission critical scientific innovation. We are excited to collaborate with Amicus and provide capital to advance their mission of bringing important new medicines to people living with rare diseases around the world."

Simon Harford, Amicus Chief Financial Officer, added: "Securing this financing with Blackstone as we launch Pombiliti™ + Opfolda™ around the world, allows us to better align our borrowing with anticipated cash flows while at the same time enhancing our ability to maximize access to our therapies for people living with rare diseases."

Source: https://ir.amicusrx.com/news-releases/news-release-details/amicus-therapeutics-and-blackstone-enter-430-million-strategic

# Insights from the Last Week's Biofuture Conference




# Biofuture Talk by Michael Dowling, CEO, Northwell


- Dowling is an Irish-born hospital administrator running one of the largest health systems in the United States.
- Northwell has 85,000 employees and is the largest employer in New York. Revenue last year was $15.6 billion.
- Dowling spoke about a range of important topics including physician burnout (he's a bit of a skeptic), the importance of social determinants of health and community outreach, the importance of recognizing and treating customers at Northwell with compassion and as consumers.
- Wants a trip to Northwell to be as good as it can be.
- Northwell has multiple Michelin-starred chefs as an example.
- He talked about leadership and courage, calling out gun violence as a health issue, when it is the no. 1 cause of death in children, surpassing auto accidents and cancer.
- Very insightful conversation bringing up real issues we need to tackle as a community to improve a healthcare system that is obviously not working and not providing the needed care to patients, while it's the one that cost the most per capita in the world.

# Biofuture Panel on the Difficult Biotech Market

***Navigating the Biotech Landscape in a Difficult Market (October 6, 2023)***

**Moderator:**

Tim Opler, PhD, Managing Director, Global Healthcare Group, Stifel

**Panelists:**

Sal Saraceno, Managing Director, Healthcare Investment, Capital One

Brad Sitko, Chief Investment Officer, XOMA

Robert Williamson, President & COO, Triumvira

Hanadie Yousef, PhD, CEO & Co-Founder, Juvena

- **Williamson**: toughest market we've seen since 1991.
- **Williamson**: Most important thing to do is to stay in touch with your investors and keep them informed on what's going on. Information and connection are critical.
- **Williamson**: Building relationships with new investors is also important. The right time to do it is when you are *not* raising money.
- **Yousef**: Raised $41mm last year. A lot more investors said no than yes but kept meeting with investors.
- **Yousef**: The most important thing is innovation and getting drugs to the clinic. Working very diligently with a computational platform that understands the relationship between secreted proteins and phenotype to create drugs.
- **Yousef**: Teamwork and culture incredibly important to being able to execute well and fast.
- **Sitko**: alternative financing options such as royalty financing are critical in this market
- **Saraceno**: optimistic about a market turn coming in 2024. Money is out there. Have to deliver what investors want.
- **Opler**: In the long run the biotech market has gone in only one direction: up. This is not going to change.

Source: https://biofuture.com/

# Industry News

# Genetic support for FDA-approved drugs over the past decade

Polina V. Rusina, Maria J. Falaguera, Juan Maria R. Romero, Ellen M. McDonagh, Ian Dunham & David Ochoa

Human genetic evidence has been reported as a proxy for the success of drugs in clinical trials owing to its ability to pinpoint causal mechanistic links between drug targets and diseases. Two-thirds of the new drugs approved by the FDA in 2021 were supported by human genetic evidence associating the intended pharmacological target or its physical interactors with the indication or a surrogate trait. Here, we expand this retrospective analysis to FDA approvals from 2013–2022. This analysis shows that currently available genetic evidence supported 63% (271 out of 428) of the new drugs approved in the past decade overall, with a range of 41–72% annually (Fig. 1). Approved drugs without obvious genetic support were often symptomatic treatments or molecules not targeting human gene products.

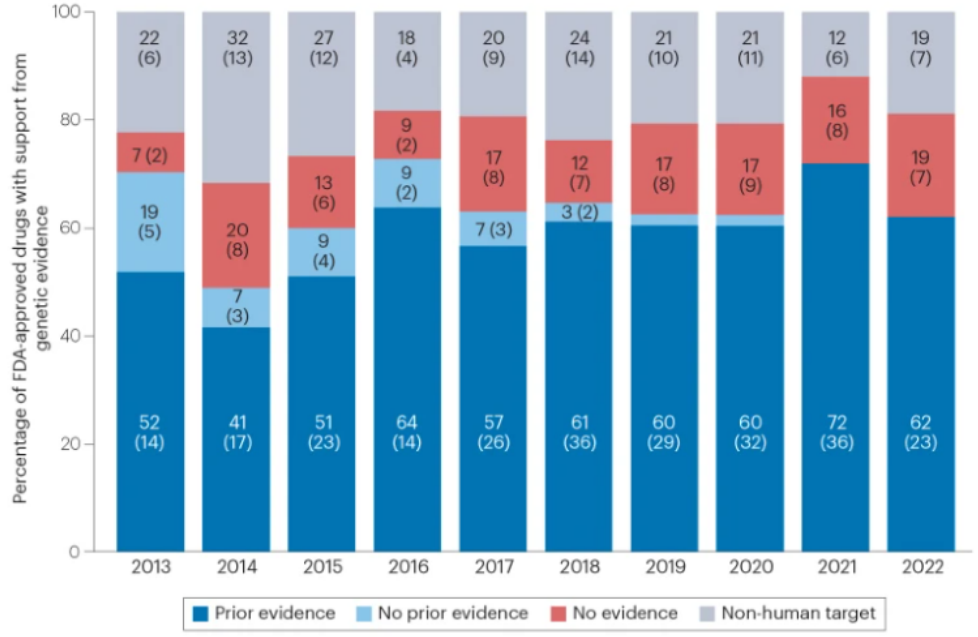



**Fig. 1 | Annual breakdown of drugs approved by the FDA from 2013 to 2022 based on the presence and timing of support from genetic evidence.** The depicted categories are drugs with prior genetic evidence, drugs with any genetic evidence, drugs without genetic evidence and drugs with non-human targets or an unknown mechanism of action. The numbers of drugs are shown in brackets. For additional data and details of the analysis, see Supplementary information. Data source: Open Targets Platform (June 2023).

Source: https://www.nature.com/articles/d41573-023-00158-x

# After Shunning Scientist, University of Pennsylvania Celebrates Her Nobel Prize

**Gregory Zuckerman, *Wall Street Journal*, October 4, 2023 (excerpt)**

"The University of Pennsylvania is basking in the glow of two researchers who this week were awarded the Nobel Prize in medicine for their pioneering work on messenger RNA.

Until recently, the school and its faculty largely disdained one of those scientists.

Penn demoted Katalin Karikó, shunting her to a lab on the outskirts of campus while cutting her pay. Karikó's colleagues denigrated her mRNA research, and some wouldn't work with her, according to her and people at the school. Eventually, Karikó persuaded another Penn researcher, Drew Weissman, to work with her on modifying mRNA for vaccines and drugs, though most others at the school remained skeptical, pushing other approaches.

Karikó hasn't only proven her detractors wrong but also reached the pinnacle of science. Her research with Weissman helped lead to the mRNA vaccines that protected people worldwide during the Covid-19 pandemic and now shows promise for flu, cancer and other diseases.

Penn, which patented their mRNA technology, has made millions of dollars from drugmakers that licensed it. And on Monday, when Karikó and Weissman were awarded the Nobel, on top of prestigious science prizes in recent years, the school expressed a different perspective on their work.

The reversal offers a glimpse of the clubby, hothouse world of academia and science, where winning financial funding is a constant burden, securing publication is a frustrating challenge and those with unconventional or ambitious approaches can struggle to gain support and acceptance. "It's a flawed system," said David Langer, who is chair of neurosurgery at Lenox Hill Hospital, spent 18 years studying and working at Penn and was Karikó's student and collaborator."

**Source**: https://www.wsj.com/health/after-shunning-scientist-university-of-pennsylvania-celebrates-her-nobel-prize-96157321

# My Love/Hate Relationship with Process

Posted October 5th, 2023

by Aoife Brennan, in Biotech startup advice, From The Trenches, Leadership

Life Sci VC

I remember vividly my first vacation with the man who would be my husband. In the days before Airbnb and on-line travel websites, he had all the books and had thoroughly researched each destination, every transport option, all the food venues. The guy clearly had process. In contrast, spontaneity was my compass. I tactfully broached the subject of maybe being more open to serendipity on our trip. He begrudgingly handed over his Lonely Planet full of page flags and told me I could choose where we would eat that evening. I flicked to the 'Where to Eat' section only to find he had already underlined and dated his top choice. If chaos is the law of nature; order is the dream of this man.

The question persists: how much process is too much when planning a vacation? This question, I've come to realize, holds relevance not just for wanderers but also for companies at all stages of their lifecycle. An oft-cited motive for biotech peers leaving their current roles is the aspiration to re-engage in the genuine work of scientific innovation and drug development, evading the trappings of bureaucracy in larger organizations. It can feel like fidelity to organizational processes supersedes the core mission itself.

Reflecting on my seven-year journey at Synlogic, I'm reminded of our nascent days in drug development. The absence of standard operating procedures, project teams, or any concrete structure was palpable. Over the years, we've grown into a clinical-stage development organization, with our lead product candidate for PKU now undergoing a pivotal clinical trial. We've established a GMP manufacturing facility, weathered an FDA inspection unscathed, and introduced and revised processes along the way. This voyage has granted me ample opportunity to ponder the intricacies of process management and glean valuable insights.

Andy Grove's description of navigating this balance of process and agile innovation during his time as CEO of Intel resonated deeply with me. As companies mature and expand, an influx of process becomes inevitable. However, maintaining adaptability in the face of unforeseen developments is equally vital. In biotech change is the only constant. Processes and infrastructure that were built for a situation that is no longer relevant need to change just as quickly. Program discontinuations and staffing cuts can be easier to accomplish than killing the sacred process cow. Grove makes the case for allowing more chaos at times of uncertainty/pivot points.

**I personally like the concept of 'minimal viable process' which involves being prepared to try things out, get feedback and reverse course on things that are not working.** Minimal viable process will be unique to each organization and may also look different for different areas in the organization - we would never expect the research team to follow the same processes as the GMP manufacturing team. Ensuring that everyone in the organization understands why is an important objective of our internal communications and training.

**Source**: https://lifescivc.com/2023/10/my-love-hate-relationship-with-process/

# New Covid Variants Don't Show Positive Tests Until Day 4 or 5 with Rapid Tests

## The New Normal: Delayed Peak SARS-CoV-2 Viral Loads Relative to Symptom Onset and Implications for COVID-19 Testing Programs

Jennifer K Frediani et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

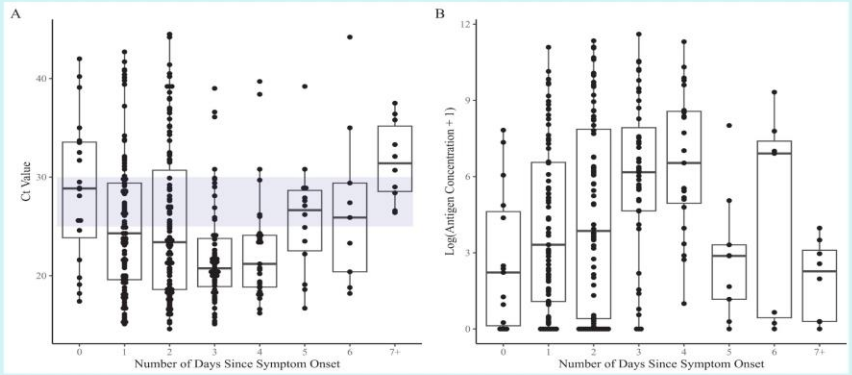
### Study Population

Symptomatic (Sx) adult patients seeking diagnostic testing for URI in GA. 91% with Hx of SARS-CoV-2 vaccination and/or infection

### Methods

Symptom duration and recent testing history recorded. Nasal swab tested by RT-PCR (SARS-CoV-2/Flu/RSV); Ct value recorded. SARS-CoV-2 nucleoprotein measured in PCR-positive samples.

### Results




In 348 newly-diagnosed individuals, SARS-CoV-2 median VL by Ct and Ag peaked on 4th/5th day of Sx. Estimated Ag rapid diagnostic test (RDT) sensitivity was 30-60% on the 1st and 80-93% on the 4th day of Sx.

**Implications for Ag RDT use: Increased effort should be made to educate the public about repeating COVID-19 Ag RDT in individuals with negative results on days 1-3 of Sx; individuals may not test positive until the 4th/5th day of Sx.**

Clinical Infectious Diseases — Full text not published yet, reference pending

Source: https://doi.org/10.1093/cid/ciad582

# uniQure Announces Strategic Reorganization to Reduce Operating Expenses and Support Advancement of Multiple Clinical-Stage Programs

**Press Release, Oct 5, 2023**

*~ Reduction of 28% of workforce not related to HEMGENIX® manufacturing obligations; Total cost savings of $180 million to extend cash runway into second quarter of 2027 ~*

*~ Discontinuing investments in more than half of research and technology projects, centralizing operations, and streamlining organization ~*

*~ Prioritizing continued development of AMT-130 in Huntington's disease and near-term initiation of clinical trials for AMT-260 in refractory mesial temporal lobe epilepsy, AMT-162 in SOD1-ALS, and AMT-191 in Fabry disease; Multiple potential value drivers expected over next two years ~*

*~ As a result of reprioritization, Ricardo Dolmetsch, Ph.D. Chief Scientific Officer to depart the Company and Rich Porter, Ph.D. Chief Business Officer will assume responsibilities for research as well as nonclinical and vector development ~*

Source: https://uniqure.gcs-web.com/news-releases/news-release-details/uniqure-announces-strategic-reorganization-reduce-operating

# Roughly 20% of Deaths Caused by Modifiable Risk Factors Linked to Cardiovascular Disease

## NEJM, October 5, 2023 (excerpt)

Among 1,518,028 participants (54.1% of whom were women) with a median age of 54.4 years, regional variations in the prevalence of the five modifiable risk factors were noted. Incident cardiovascular disease occurred in 80,596 participants during a median follow-up of 7.3 years (maximum, 47.3), and 177,369 participants died during a median follow-up of 8.7 years (maximum, 47.6). For all five risk factors combined, the aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease was 57.2% (95% confidence interval [CI], 52.4 to 62.1) among women and 52.6% (95% CI, 49.0 to 56.1) among men, and the corresponding values for 10-year all-cause mortality were 22.2% (95% CI, 16.8 to 27.5) and 19.1% (95% CI, 14.6 to 23.6).

Harmonized individual-level data from a global cohort showed that 57.2% and 52.6% of cases of incident cardiovascular disease among women and men, respectively, and 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to five modifiable risk factors.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2206916

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

### Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality

Global Cardiovascular Risk Consortium DOI: 10.1056/NEJMoa2206916

**CLINICAL PROBLEM**

Five modifiable risk factors — body-mass index (BMI), systolic blood pressure, non–high-density lipoprotein (non-HDL) cholesterol level, current tobacco smoking, and diabetes — are associated with cardiovascular disease and death from any cause. Studies using individual-level data to evaluate the regional and sex-specific associations of these risk factors with the development of cardiovascular disease are lacking.

**STUDY DESIGN**

A pooled analysis harmonized individual-level data from 112 cohort studies conducted in 34 countries and 8 geographic regions including 1,518,028 participants (median age, 54.4 years) to assess the effects of the five risk factors mentioned above on the 10-year incidence of cardiovascular disease and death from any cause.

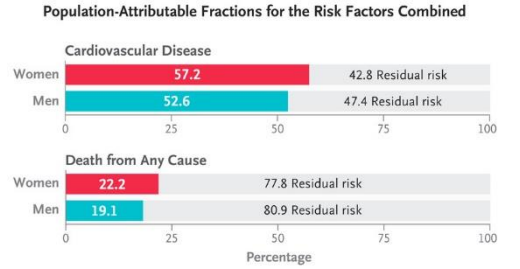
**RESULTS**

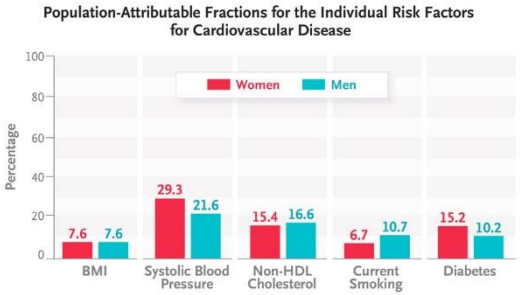
The prevalence of the five risk factors and the incidence of cardiovascular disease and death from any cause varied across geographic regions worldwide, with women having consistently lower event rates than men. For both men and women, more than half the cases of incident cardiovascular disease and one fifth of deaths may be attributable to the five risk factors. Among the risk factors, elevated systolic blood pressure appeared to be the largest contributor to the population-attributable fraction of cardiovascular disease events.

**LIMITATIONS AND REMAINING QUESTIONS**

- The cohorts included in the study varied with respect to definitions of end points, how the data were collected, and the quality and quantity of data.
- The effects of overweight and obesity may be mediated by hyperlipidemia, hypertension, and diabetes.
- Smoking cessation during follow-up might have led to an underestimation of smoking as a risk factor.

**Links: Full Article | NEJM Quick Take | Editorial**


**CONCLUSIONS**

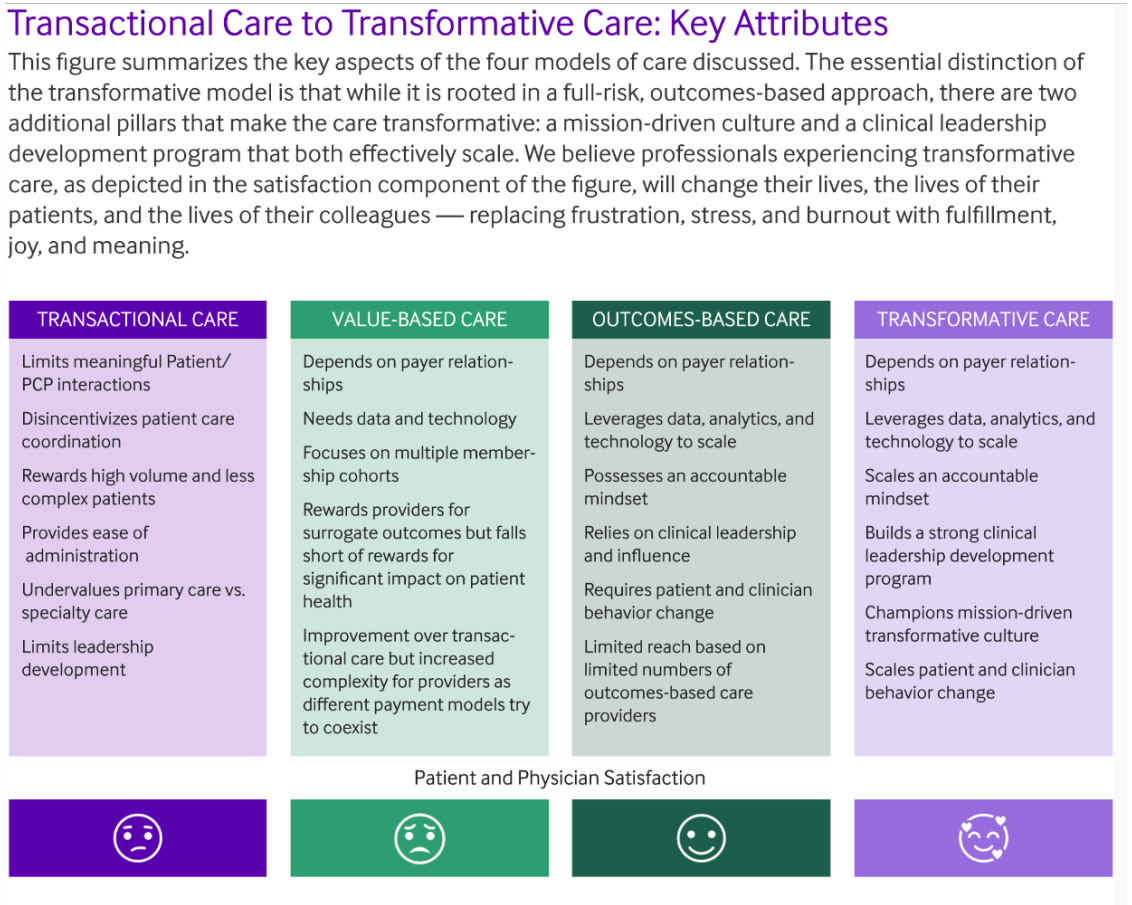
**Harmonized individual-level data from a global cohort showed that over 10 years, more than half the cases of incident cardiovascular disease and one fifth of deaths in adults may be attributable to five modifiable risk factors.**

# The Case for Transformative Care

**A new primary care delivery model relies on clinician influence to obtain better health outcomes.**

Gordon Chen and Chris Chen, Chenmed, *NEJM Catalyst*, October 5, 2023 (excerpt)

The U.S. health care system's revenue structure includes payment models that are incompatible with each other and the needs of consumers: the transactional fee-for-service model and variations of value-based and outcome-based care models. While provider organizations struggle to function in these environments, physician leaders at ChenMed contend delivery systems can move beyond these confusing and ineffective models of care and embrace a transformative care model. Transformative care combines a capitation payment model and a primary care delivery approach that emphasizes care team accountability for patient care and requires care team members to develop the trust-building and influencing skills necessary to modify patient behavior and create better health outcomes. The success of the model is based on scaling and sustaining outcomes-based care and supporting clinicians in their mission to focus on quality patient care and positive health outcomes. Key components of the model include: robust data and technology to understand patient needs and to measure progress; prioritized physician/patient relationships and a mindset of accountability to ensure the necessary time and resources are invested in developing the trust and influence with patients required to improve outcomes; and personal development programs that start in medical school, continue at the clinic level, and emphasize self-evaluation, behavior modification, mentorship, peer-to-peer feedback, expanding care capacity through the development of others, and a daily commitment to maintain and pursue excellence.




Source: https://catalyst.nejm.org/doi/full/10.1056/CAT.23.0115

HEALTH AFFAIRS FOREFRONT | ACCOUNTABLE CARE FOR POPULATION HEALTH

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# Making The Promise Of Value-Based Care Meaningful To Consumers

Jocelyn Frye, Frederick Isasi, Emily Stewart

OCTOBER 5, 2023 10.1377/forefront.20231003.828036


Over the past decade, health care providers and insurance plans have increasingly pursued value-based care models that are designed to improve patient and clinician experiences while reducing costs and improving quality to produce better population health. With more community and consumer engagement, these models have huge potential for advancing key consumer priorities, including affordability, effective care coordination and communication, data sharing, and providing whole-person care. However, progress has been relatively slow, and the opportunity to engage patients in their care has not yet been fully realized. As value-based care models continue to improve and evolve, the definition of "value" for consumers and patients must also be broadened to include reducing inequities in access and quality.

In recent years, health care payers and professionals have leveraged value-based payment models to address health care disparities that perpetuate in the fee-for-service system and that undermined some communities' health long before COVID-19. These models aim to address disparities by improving quality of care and incentivizing providers to partner with community-based services and workers beyond traditional clinical care.

It is well-documented that 80 percent to 90 percent of drivers of health are rooted in socioeconomic and environmental factors including structural inequities, often referred to as the social determinants of health. However, in fee-for-service medicine, payments to physicians are almost exclusively tied to medical and clinical care (with incentives to maximize service volume), which are not necessarily aligned with the non-clinical needs that affect health outcomes. Many alternative payment models use fee-for-service as an underlying payment method. However, additional model design elements including care management fees, shared savings arrangements, and capitated payment can allow health care professionals to invest in services and benefits that extend beyond the clinic walls to respond to social needs affecting people's health.

Source: https://www.healthaffairs.org/content/forefront/making-promise-value-based-care-meaningful-consumers

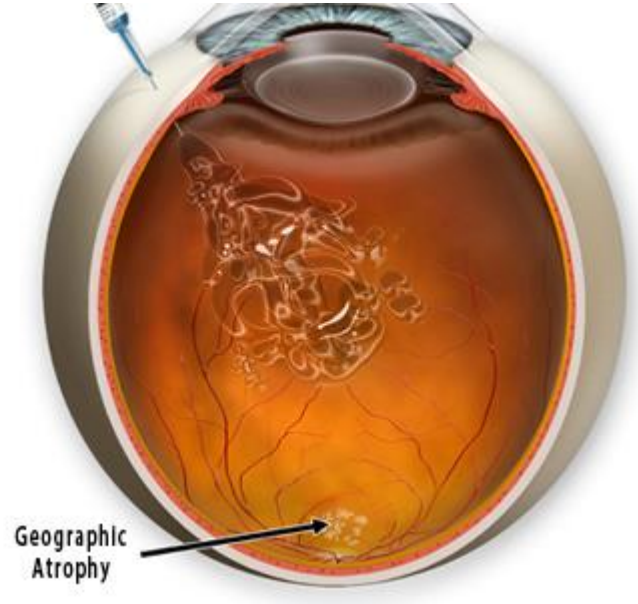
# Apellis Announces Preliminary U.S. Net Revenues of Approximately $74 Million for SYFOVRE® (pegcetacoplan injection) in the Third Quarter of 2023

**WALTHAM, Mass., Oct. 05, 2023 (GLOBE NEWSWIRE)** -- Apellis Pharmaceuticals, Inc. (Nasdaq: APLS) today provided an update on the launch of SYFOVRE® (pegcetacoplan injection) for geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

"In only seven months, more than 100,000 vials have been shipped to physician practices, which we believe is a testament to the unmet need and the strength of SYFOVRE's product profile. SYFOVRE offers increasing treatment effects over time with as few as six doses per year," said Adam Townsend, chief commercial officer, Apellis. "It is very encouraging to see the return to weekly growth in demand as physicians and patients have learned more about the long-term efficacy from the GALE study and real-world safety of SYFOVRE. With our permanent J-code now in place, we look forward to building on these trends and continuing to bring SYFOVRE to people living with this chronic disease."

*Strong growth in demand*

1. Apellis expects approximately $74 million in preliminary U.S. net product revenue for SYFOVRE in the third quarter and approximately $160 million in preliminary total U.S. net product revenue for SYFOVRE since launch in March 2023 through September 30, 2023.
2. Approximately 37,000 commercial vials and 10,000 samples were distributed to physician practices in the third quarter; more than 100,000 total vials have been delivered to date.
3. Continued strong demand; week-over-week growth returned starting in August, with weekly orders from both new and existing sites of care.




Source: https://investors.apellis.com/news-releases/news-release-details/apellis-announces-preliminary-us-net-revenues-approximately-74

# Takeda Pulls Exkivity

**Madeline Armstrong, *Oncology Pipeline*, Oct 3, 2023 (excerpt)**

The US withdrawal of Takeda's tyrosine kinase inhibitor Exkivity on Monday was just the latest example of the FDA's accelerated approval clampdown.

The news should be another warning to companies that have taken advantage of this fast track, but whose products have later shown to have toxicity or lacklustre efficacy – or both. A look at other recent withdrawals suggests that the FDA is taking a particularly hard stance in uses where other options are available.

**Notable Oncology Product Withdrawals**

| Product | Company | Indication | Accelerated approval | Withdrawal details |
|---|---|---|---|---|
| Exkivity | Takeda | 2L EGFR Exon 20 insertion+ NSCLC | Sep-21 | Withdrawn Oct 2023 after failing Exclaim-2 |
| Blenrep | GSK | >5L relapsed/refractory multiple myeloma | Aug-20 | Withdrawn Nov 2022 after failing Dreamm-3 |
| Tecentriq | Roche | 1L urothelial cancer | Apr 2017 (label narrowed Jul 2018) | Withdrawn Nov 2022 after failing Imvigor-130 (2L use already withdrawn Mar 2021) |
| Ukoniq | TG Therapeutics | 2L MZL & 4L FL | Feb-21 | Withdrawn Apr 2022 on toxicity concerns |
| Zydelig | Gilead | 3L FL & SLL | Jul-14 | Withdrawn Jan 2022, company citing confirmatory trial enrolment challenges |
| Copiktra | Secura Bio | 3L FL | Sep-18 | Withdrawn Dec 2021 after confirmatory trial plans abandoned |
| Tecentriq | Roche | 1L TNBC | Mar-19 | Withdrawn Aug 2021 after failing Impassion-131 |
| Keytruda | Merck & Co | 3L gastric/GEJ adenocarcinoma | Sep-17 | Withdrawn Jul 2021 after failing Keynote-061 |
| Opdivo | Bristol Myers Squibb | 2L liver cancer | Sep-17 | Withdrawn Jul 2021 after failing Checkmate-459 |
| Keytruda | Merck & Co | 3L SCLC | Jun-19 | Withdrawn Mar 2021 after failing Keynote-604 |
| Imfinzi | AstraZeneca | 2L urothelial cancer | May-17 | Withdrawn Feb 2021 after failing Danube |
| Opdivo | Bristol Myers Squibb | 3L SCLC | Aug-18 | Withdrawn Dec 2020 after failing CheckMate-451 &331 |

Source: https://www.oncologypipeline.com/apexonco/lumakras-next-test-fdas-hardening-stance

# Confirmatory Trial Trouble in KRAS

**Derek Lowe, *Science*, Oct 5, 2023 (excerpt)**

I wrote last year about KRAS-targeting drugs as cancer therapies, and that pretty much means G12C-KRAS targeting ones. That's because years of effort had yielded no solid candidates for inhibiting "plain" KRAS in tumors, but a great deal of hard work has paid off in compounds that target one of the mutant forms of it that shows up, where a glycine at position 12 has turned into a cysteine.

Amgen got a conditional approval in 2021 for the first one of these (sotorasib, or Lumakras). And as all drug-development fans will appreciate, that means that the company is required to run a confirmatory trial. Well, that trial (CodeBreaK 200, an open-label one with 345 patients) has been run, Amgen has been presenting the results from it this summer, the new data are up for FDA review, and now things are really hitting the huge high-speed industrial fan. If you're a subscriber to Stat, this article from Tuesday went into excellent detail - otherwise, read on.

If you read Amgen's press releases from the last two or three months and then read [the FDA briefing], you will feel as if you have stepped through a portal into another dimension. Unfortunately, that new world may be the one that the rest of have agreed to be the real one. Which means that the Amgen Press Release World starts to look pretty tenuous.

Here's why I say that:

1. The FDA notes first that the median progression-free survival (PFS) in this new trial was five weeks. But the standard imaging interval is six weeks, which makes you wonder how robust that five-week estimate is, given the mismatch in the data collection. And in fact, it's not so robust at all - even Amgen says in its submission that the median PFS might be as little as five days. If you're not sure which of those it is, then you're not sure if your drug works.

2. The control arm of the study (doclataxel treatment) had 23 patients who were randomized but were never actually dosed. There were only 2 such patients in the Lumakras arm, and that's enough of a discrepancy to make you wonder about systemic bias in the results.

3. The FDA reviewers say that in their opinion the clinicians evaluated the progression of cancer in these patients in ways that favored Lumakras. Remember, this was an open-label trial: the clinicians knew which patients were getting which drug, and open-label trials are open invitations to both conscious and unconscious bias in such calls. Now, this trial did have blinded independent central review (BICR) independent of these physicians, but the FDA notes that there were notably more early calls of PFS for Lumakras by the investigators as compared to the BICR and more late calls of PFS for the control patients. Ideally, such disagreements should have a more random distribution.

Source: https://www.science.org/content/blog-post/confirmatory-trial-trouble-kras

# Preliminary Phase 1 Dose-Escalation Data from ALKOVE-1 Trial of NVL-655 Demonstrated Activity in Heavily Pre-Treated Patients with ALK-Positive NSCLC

**CAMBRIDGE, Mass., Oct. 4, 2023** /PRNewswire/ -- Nuvalent, Inc. (Nasdaq: NUVL), a clinical-stage biopharmaceutical company focused on creating *precisely* targeted therapies for clinically proven kinase targets in cancer, today announced preliminary data from the Phase 1 dose-escalation portion of its ongoing ALKOVE-1 Phase 1/2 clinical trial of NVL-655 for patients with advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors as reported in an abstract accepted for presentation at the 35th AACR-NCI-EORTC (ANE) Symposium in Boston, Massachusetts. Updated preliminary data will be presented at the conference and during a live webcast and conference call with management on October 13th at 8:00am EDT.

NVL-655 is a novel brain-penetrant ALK-selective tyrosine kinase inhibitor (TKI) created with the aim to simultaneously overcome the clinical challenges of emergent treatment resistance, brain metastases, and off-target central nervous system (CNS) adverse events associated with tropomyosin receptor kinase (TRK) inhibition that may limit the use of currently available ALK TKIs.

NVL-655 is currently being evaluated in the ALKOVE-1 Phase 1/2 clinical trial, a first-in-human study of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors (NCT05384626). The Phase 1 dose escalation portion is enrolling ALK-positive NSCLC patients who have previously received at least one ALK TKI and patients with other ALK-positive solid tumors who have been previously treated with at least one prior systemic anticancer therapy. The primary objectives are to determine the recommended Phase 2 dose (RP2D) and if applicable, the maximum tolerated dose (MTD) of NVL-655 in patients with ALK-positive solid tumors. Additional objectives include characterization of the overall safety, tolerability, and pharmacokinetic profile, and evaluation of the preliminary anti-tumor activity of NVL-655.

Preliminary activity of NVL-655 was demonstrated in this heavily pre-treated patient population as measured by objective response rate (ORR) per RECIST 1.1. Partial responses were observed in 45% (15/33; 8 pending confirmation) of response-evaluable patients with ALK-positive NSCLC who received NVL-655 at doses ranging from 15-150 mg once daily. An ORR of 65% (11/17) was observed in patients with baseline ALK resistance mutations, and an ORR of 41% (12/29) was observed in patients post-lorlatinib, including cases with compound resistance mutations. Early indicators of CNS activity were also observed.

**These data for Nuvalent's ALK inhibitor created a strong positive market reaction (shares up 40%).**

**In a year where, with a few exceptions, oncology biotechs are being punished, Nuvalent has shined.**

**What's impressive is that the company's ALK program has potential to be successful in second-line and front-line settings on NSCLC ALK-positive cancers.**

**The combination of a strong dataset in a large oncology market is exceptional in today's biotech marketplace.**

Source: https://investors.nuvalent.com/2023-10-04-Preliminary-Phase-1-Dose-Escalation-Data-from-ALKOVE-1-Trial-of-NVL-655-Demonstrated-Activity-in-Heavily-Pre-Treated-Patients-with-ALK-Positive-NSCLC-and-an-ALK-Selective,-TRK-Sparing-Safety-Profile

# ALX Oncology Reports Positive Interim Phase 2 ASPEN-06 Clinical Trial Results of Evorpacept for the Treatment of Advanced HER2-Positive Gastric Cancer

**SOUTH SAN FRANCISCO, Calif., Oct. 03, 2023 (GLOBE NEWSWIRE)** -- ALX Oncology Holdings Inc., an immuno-oncology company developing therapies that block the CD47 immune checkpoint pathway, today announced positive prespecified interim Phase 2 data from its ASPEN-06 clinical trial, a randomized multi-center international study evaluating evorpacept, the Company's CD47 blocking therapeutic, in combination with trastuzumab, CYRAMZA® (ramucirumab) and paclitaxel for the treatment of patients with HER2-positive gastric/gastroesophageal junction ("GEJ") cancer. This prespecified interim analysis represents results from 54 randomized patients with second and third line gastric/GEJ cancer, including a meaningful number of patients previously treated with ENHERTU® (trastuzumab deruxtecan) and checkpoint inhibitors. Patients were treated with evorpacept at 30 mg/kg every two weeks, mirroring the treatment cycle of trastuzumab, CYRAMZA and paclitaxel.

**Phase 2 ASPEN-06 Interim Analysis Results:**

- A confirmed overall response rate ("ORR") of 52% was demonstrated for evorpacept in combination with trastuzumab + CYRAMZA + paclitaxel compared to 22% for the control group of trastuzumab + CYRAMZA + paclitaxel.
- Median duration of response ("mDOR") was not reached for the evorpacept combination treatment arm compared to 7.4 months for the control group.
- The safety profile of evorpacept was consistent with previous clinical trials and was well-tolerated.
- These interim results compare favorably to the efficacy reported for CYRAMZA + paclitaxel in the RAINBOW study (ORR of 28% and mDOR of 4.4 months), which is the regulatory benchmark and global standard of care for second line gastric/GEJ cancer.

**It's been a long time since we have seen a positive dataset with a CD47 inhibitor.**

**A number of observers and analysts have been skeptical about the results shown here – perhaps because of the many past clinical failures with CD47 targeted agents.**

**Nonetheless, the difference in ORR and the lack of reach of mDOR is indeed impressive.**

Source: https://ir.alxoncology.com/news-releases/news-release-details/alx-oncology-reports-positive-interim-phase-2-aspen-06-clinical

# Syndax Announces Pivotal AUGMENT-101 Trial of Revumenib in Relapsed/Refractory KMT2Ar Acute Leukemia Meets Primary Endpoint

**WALTHAM, Mass., Oct. 2, 2023 /PRNewswire/**-- Syndax Pharmaceuticals (Nasdaq: SNDX), a clinical-stage biopharmaceutical company developing an innovative pipeline of cancer therapies, today announced positive topline data from the protocol-defined pooled analysis of the pivotal AUGMENT-101 trial of revumenib, a first-in-class menin inhibitor, in adult and pediatric patients with relapsed/refractory (R/R) KMT2A-rearranged (KMT2Ar) acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL).

The AUGMENT-101 trial met its primary endpoint at the protocol-defined interim analysis stage with a complete remission (CR) or a CR with partial hematological recovery (CRh) rate of 23% (13/57; 95% confidence interval [CI]: [12.7, 35.8, one-sided p-value = 0.0036]) among the 57 efficacy evaluable patients in the pooled KMT2Ar acute leukemia cohort. The CR/CRh rate in patients with KMT2Ar AML was 24.5% (12/49). The CR/CRh responses in both the overall population and the AML subset were durable with a 6.4-month (95% CI: 3.4, NR) median duration as of the July 24, 2023 data cut-off, with 46% (6/13) remaining in response. Minimal residual disease (MRD) status was assessed in 10 of the 13 patients who achieved a CR/CRh, 70% (7/10) of whom were MRD negative.

In the efficacy-evaluable patients, the overall response rate1 was 63% (36/57; 95% CI: [49.3, 75.6]). A total of 14 (39%) patients who achieved an overall response underwent hematopoietic stem cell transplant (HSCT), eight of whom did not achieve a CR or CRh prior to transplant. Half (7/14) of the patients who had an HSCT received post-transplant maintenance with revumenib and three additional patients (3/14; 21%) were in follow-up and are eligible to restart revumenib as post-transplant maintenance.

Based on the Independent Data Monitoring Committee (IDMC) recommendation, the Company is stopping the trial to further accrual in the KMT2Ar cohorts. Syndax continues to expect to submit an NDA for revumenib for the treatment of R/R KMT2Ar acute leukemia to the U.S. Food and Drug Administration (FDA) by year-end.

**Recent industry conversations highlight the utility of Revumenib should it be approved by FDA.**

**Many patients with AML receive a transplant and revumenib is a particularly interesting therapy to use in the post-transplant setting to manage the risk of disease recurrence.**

**Another question is whether the observed CR/CRh duration seen in this study was long enough to medically beneficial.**

**Our understanding is the hem/onc's generally believe that it is.**

Source: https://ir.syndax.com/news-releases/news-release-details/syndax-announces-pivotal-augment-101-trial-revumenib

# Ozempic for Weight Loss Is Disrupting Companies' Business Models

**Leslie Patton, *Bloomberg*, Oct 7, 2023 (excerpt)**


As sales of appetite-suppressing drugs such as Ozempic and Mounjaro skyrocket, Corporate America is grappling with the question: How does a less-hungry, less-impulse-prone consumer affect my business model?

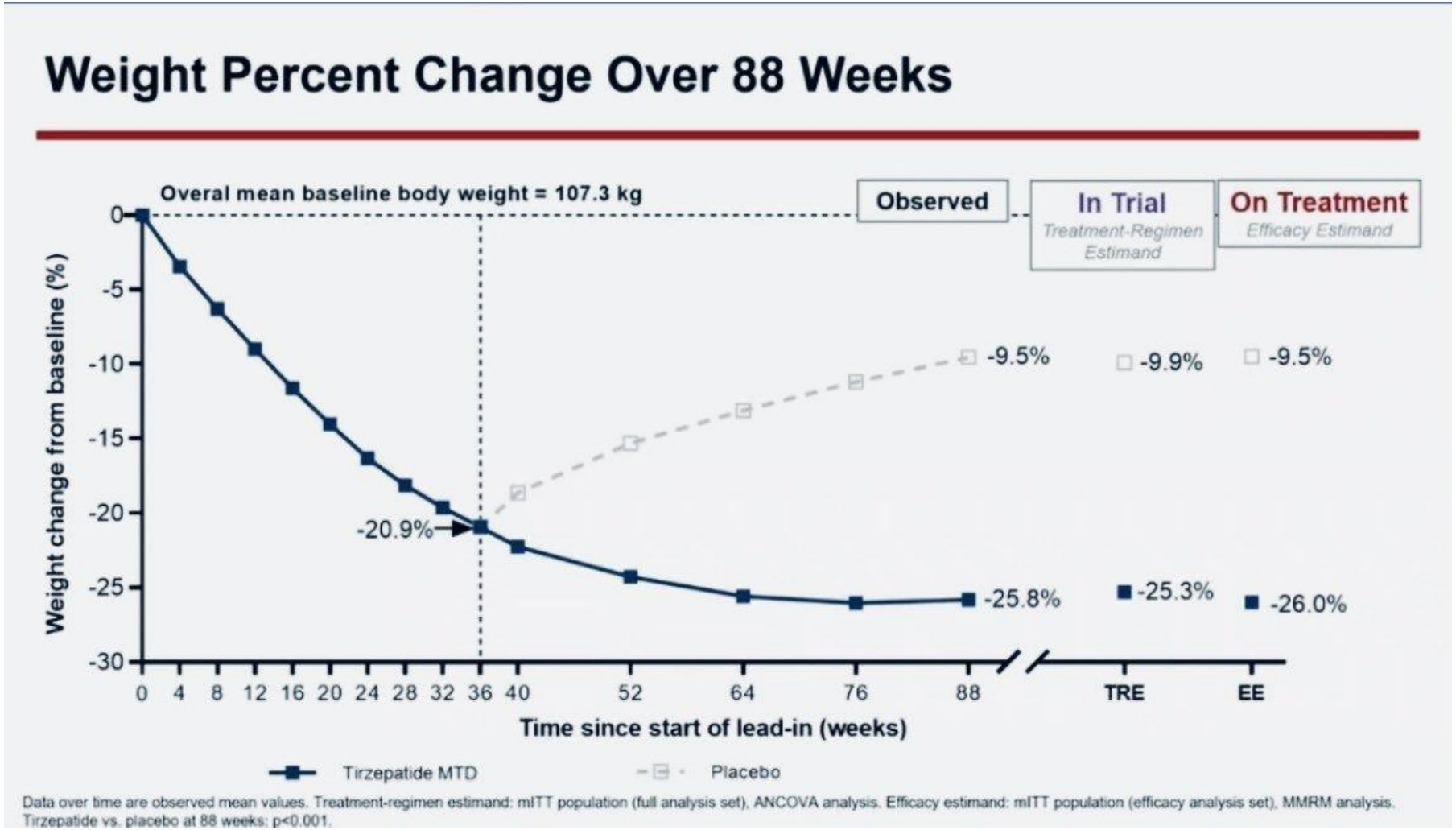
Companies from Walmart Inc. to Conagra Brands Inc. are weighing how much to factor the diabetes drugs known as GLP-1s, increasingly being used for weight loss, into their strategies. Moves they make now could reverberate for years to come, so the pressure's high to get it right.

"Companies will overreact. The smart money will take action, but act slowly," said Gary Stibel, chief executive officer of New England Consulting Group, which advises consumer and health-care companies.

John Furner, CEO of Walmart's US operations, recently said the retailer is seeing a "slight pullback in the overall basket" of food purchases as a result of the drugs, but added it's too early to draw definitive conclusions. Conagra CEO Sean Connolly told investors this week that his company's scientists are looking at the data, and the maker of Slim Jim and Swiss Miss could offer smaller portions in the coming years if that's the way preferences evolve.

Source: https://www.bloomberg.com/news/articles/2023-10-07/ozempic-for-weight-loss-is-disrupting-companies-business-model

# At EASD Lilly Shows that Tirzepatide Cessation Leads to Rebound But Some Weight Stays Off




**SURMOUNT-4 study at EASD2023**

In the first 36 weeks on the SURMOUNT-4 study, all patients got Tirzepatide followed by 52-week randomization to Tirzepatide or placebo. At the end of 88 weeks: -the Tirzepatide arm lost 26% of their body weight while the placebo arm saw weight rebound, but patients still ended 9.5% below their starting weight.

October 5, 2023 JAMA

# Risk of Gastrointestinal Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss

Mohit Sodhi, MSc[1]; Ramin Rezaeianzadeh, BSc[1]; Abbas Kezouh, PhD[2]; et al

Our cohort included 4144 liraglutide, 613 semaglutide, and 654 bupropion-naltrexone users. Incidence rates for the 4 outcomes were elevated among GLP-1 agonists compared with bupropion-naltrexone users. For example, incidence of biliary disease (per 1000 person years) was 11.7 for semaglutide, 18.6 for liraglutide, and 12.6 for bupropion-naltrexone and 4.6, 7.9, and 1.0, respectively, for pancreatitis.

**Use of GLP-1 agonists compared with bupropion naltrexone was associated with increased risk of pancreatitis (adjusted HR, 9.09), bowel obstruction (HR, 4.22), and gastroparesis (HR, 3.67)** but not biliary disease (HR, 1.50 [95% CI,0.89-2.53]).

Table 2. Risks of Biliary Disease, Pancreatitis, Bowel Obstruction, and Gastroparesis Among Users of GLP-1 Agonists vs Bupropion-Naltrexone

| Outcomes | GLP-1 agonists, HR (95% CI)[a] Crude | Adjusted[b] | Bupropion-naltrexone |
|---|---|---|---|
| **Primary analysis** | | | |
| Biliary disease | 1.48 (0.88-2.47) | 1.50 (0.89-2.53) | 1 [Reference] |
| Pancreatitis | 10.33 (1.44-74.40) | 9.09 (1.25-66.00) | 1 [Reference] |
| Bowel obstruction | 5.16 (1.27-21.00) | 4.22 (1.02-17.40) | 1 [Reference] |
| Gastroparesis | 3.31 (1.04-10.50) | 3.67 (1.15-11.90) | 1 [Reference] |
| **Sensitivity analyses** | | | |
| Exclusion of hyperlipidemia | | | |
| Biliary disease | 1.50 (0.88-2.56) | 1.46 (0.84-2.51) | 1 [Reference] |
| Pancreatitis | 9.80 (1.36-70.79) | 7.99 (1.10-58.30) | 1 [Reference] |
| Bowel obstruction | 4.43 (1.08-18.20) | 3.63 (0.87-15.10) | 1 [Reference] |
| Gastroparesis | 3.32 (1.04-10.60) | 3.67 (1.14-11.80) | 1 [Reference] |
| Analysis with less-restrictive obesity definition[c] | | | |
| Biliary disease | 1.29 (0.92-1.80) | 1.20 (0.85-1.69) | 1 [Reference] |
| Pancreatitis | 6.19 (1.99-19.30) | 5.94 (1.90-18.60) | 1 [Reference] |
| Bowel obstruction | 3.11 (1.28-7.54) | 2.44 (1.00-5.95) | 1 [Reference] |
| Gastroparesis | 2.11 (1.09-4.09) | 2.35 (1.20-4.58) | 1 [Reference] |
| E-values for adjusted HRs[d] | | | |
| Biliary disease | 2.36 | | |
| Pancreatitis | 17.67 | | |
| Bowel obstruction | 7.91 | | |
| Gastroparesis | 6.80 | | |

Abbreviations: GLP-1, glucagon-like peptide 1; HR, hazard ratio.

[a] Either semaglutide or liraglutide user.

[b] Hazard ratios adjusted for by age, sex, alcohol use, smoking, hyperlipidemia, and abdominal surgery in the last 30 days.

[c] Analysis that included patients without a diabetes code with or without an obesity code.

[d] E-values represent the HRs for the association of an unmeasured confounder (in this study's case, body mass index) with GLP-1 agonists and the study's 4 outcomes. E-values with HRs at least 2 suggest that such confounders are unlikely to change study results.

Source: https://jamanetwork.com/journals/jama/fullarticle/2810542

# EASD: Mounjaro Secret - The GIPR Agonist Substantially Improves Drug Tolerability

P-648

## A Long-Acting Glucose-Dependent Insulinotropic Polypeptide Receptor Agonist Improves Gastrointestinal Tolerability of Glucagon-Like Peptide-1 Receptor Agonist Therapy

Filip K. Knop[1-3], Shweta Urva[4], Mallikarjuna Rettiganti[4], Charles T. Benson[4], William C. Roell[4], Kieren J. Mather[4], Axel Haupt[4], Edward Pratt[4]

[1]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, [2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, [3]Steno Diabetes Center Copenhagen, Herlev, Denmark, [4]Eli Lilly and Company, Indianapolis, USA

### OBJECTIVE

- To evaluate if the long-acting GIP receptor agonist LY3537021 (LY) can improve the tolerability profile of liraglutide, a selective GLP-1R agonist

### CONCLUSIONS

**Pre-treatment with the long-acting GIPR agonist, LY, improves GI adverse events associated with rapid dose escalation of liraglutide in healthy participants**

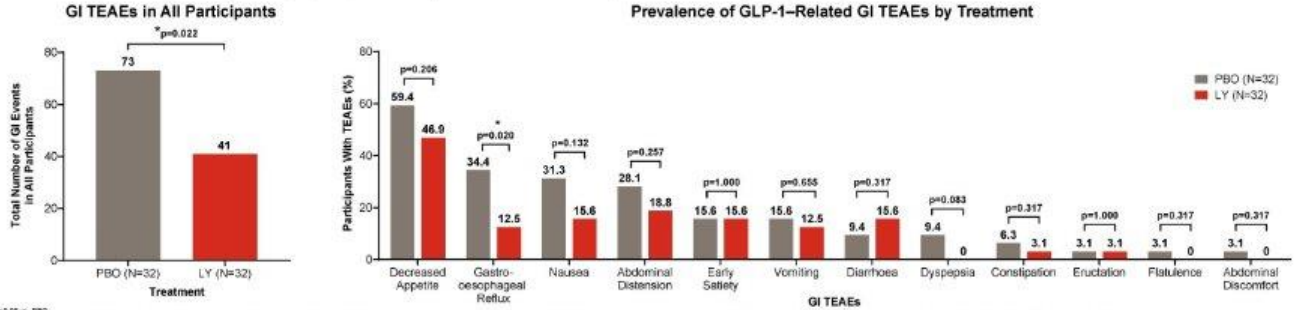
- Treatment with LY lowered liraglutide-induced GI adverse events, compared with PBO, in healthy participants
- These results demonstrate that long-acting GIPR agonism can modulate GI adverse events induced by GLP-1, possibly contributing to the clinical benefits noted with GIPR/GLP-1R co-agonism

European Association for the Study of Diabetes 2023; Hamburg, Germany; 2 – 6 October 2023

### KEY RESULTS

**LY Reduces GLP-1–Related GI Adverse Events**

- The total number of GLP-1–related GI treatment-emergent adverse events (TEAEs) in all participants was reduced with LY compared with PBO
- The mean number of GI TEAEs per participant was reduced with LY (1.28 events) compared with PBO (2.28 events)
- The percentage of participants affected by gastro-oesophageal reflux was significantly lower for LY compared with PBO
- There were nominal reductions in the percentage of participants who experienced TEAEs with LY compared with PBO, except for early satiety, diarrhoea and eructation

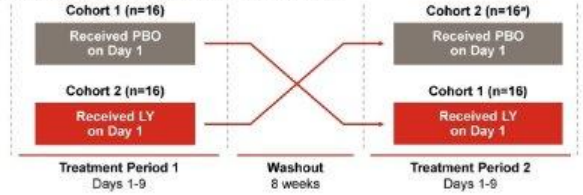



### BACKGROUND

- Tirzepatide, a long-acting glucose-dependent insulinotropic polypeptide receptor (GIPR) and glucagon-like peptide-1 receptor (GLP-1R) agonist, has shown superior efficacy for the treatment of type 2 diabetes (T2D) compared with selective GLP-1R agonism[1]
- We are evaluating a selective, long-acting GIPR agonist (LY3537021 [LY]) for the once-weekly treatment for people with diabetes and/or obesity
  - LY reduced both fasting plasma glucose and body weight in people with T2D[2]
  - LY attenuated GLP-1–related gastrointestinal (GI) side effects in preclinical models[3]
  - The long half-life of LY (approximately 14 days) supports once-weekly dosing

### STUDY DESIGN

- Phase 1, randomised, placebo (PBO)-controlled, double-blind, crossover study
- Participants were pre-treated with a single dose of LY or PBO on Day 1
- Escalating daily doses of liraglutide induces GLP-1–related GI symptoms
- The frequency of GI-related adverse events was measured




**Treatment Period Dosing Schedule**

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 |
|---|---|---|---|---|---|---|---|---|
| PBO or LY | Lira 0.6 mg | Lira 1.2 mg | Lira 1.8 mg | | Lira 2.4 mg per day (Days 5-9) | | | |

*Denotes withdrawal of 1 participant (before treatment commenced) due to scheduling conflicts.
Notes: LY was dosed at 25 mg. All subcutaneous injections were given at the clinical research unit.

### DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- During the liraglutide daily dose escalation, 2 participants in the PBO treatment period needed a slower up-titration due to GI effects

**Baseline Characteristics of Healthy Participants (N=32)**

| Characteristic | PBO in Treatment Period 1 (Cohort 1, n=16) | LY in Treatment Period 1 (Cohort 2, n=16) |
|---|---|---|
| Age, years, mean (SD) | 42.3 (9.8) | 40.3 (7.9) |
| Male, n (%) | 15 (93.8) | 16 (100.0) |
| Asian, n (%) | 15 (93.8) | 15 (93.8) |
| Weight, kg, mean (SD) | 82.2 (14.6) | 85.0 (15.7) |
| Range | 62.5-117.4 | 67.4-117.1 |
| BMI, kg/m², mean (SD) | 28.6 (4.3) | 29.0 (3.8) |
| Range | 23.3-39.1 | 24.0-37.3 |

Notes: Cohort 1 received PBO in Treatment Period 1 and LY in Treatment Period 2. Cohort 2 received LY in Treatment Period 1 and PBO in Treatment Period 2.

References
1. Frias JP, et al. Lancet. 2018;392:2180-2193.
2. Knop FK, et al. Poster presented at: ADA 2023. Poster 56-OR.
3. Samms RJ, et al. Diabetes. 2022;71:1410-1423.

Abbreviations: BMI=body mass index; GI=gastrointestinal; GIP=glucose-dependent insulinotropic polypeptide receptor; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; Lira=liraglutide; LY=LY3537021; MedDRA v 22=Medical Dictionary for Regulatory Activities version 23; N=number of participants; PBO=placebo; SD=standard deviation; T2D=type 2 diabetes; TEAE=treatment-emergent adverse event

Disclosures: F. K. Knop has served in a consulting role for: 89bio, Altimmune, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma and Zucara Therapeutics; has received grants from: Novo Nordisk and Zealand Pharma; has received honorarium from: 89bio, Altimmune, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma and Zucara Therapeutics; has received lecture fees and/or other fees from: 89bio, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, Sanofi and Zealand Pharma; has received non-financial support from: Bayer Pharmaceuticals and Novo Nordisk; is a minority shareholder of: Antag Therapeutics; and is a co-owner of the weight loss clinic, Medicinsk Vægttabsbehandling ApS. S. Urva, M. Rettiganti, C. T. Benson, W. C. Roell, K. J. Mather, A. Haupt and E. Pratt are employees and shareholders of Eli Lilly and Company
Medical writing assistance for this poster was provided by Nilisha Fernando, PhD, and Janelle Keys, PhD, CMPP, of Envision Pharma Group and was funded by Eli Lilly and Company

# Vertex Presents Positive, Updated VX-880 Results From Ongoing Phase 1/2 Study in Type 1 Diabetes at the European Association for the Study of Diabetes 59th Annual Meeting

**October 3, 2023, BOSTON**--(BUSINESS WIRE)--Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today presented longer-term data on patients dosed in Parts A and B of its Phase 1/2 clinical trial of VX-880, an investigational stem cell-derived, fully differentiated islet cell therapy in people with type 1 diabetes (T1D) with impaired hypoglycemic awareness and severe hypoglycemic events (SHEs). Prior to VX-880 treatment, all six patients enrolled had long-standing T1D with no endogenous insulin secretion, required an average of 34.0 units of insulin per day, and had a history of recurrent severe hypoglycemic events (SHEs) in the year prior to screening.

All patients in Part A and B now have more than 90 days of follow-up and have demonstrated islet cell engraftment and endogenous glucose-responsive insulin production on the Day 90 mixed-meal tolerance test (MMTT). All patients demonstrated improved glycemic control across all measures, including decreases in HbA1c, improved time-in-range on continuous insulin monitoring, and reduction or elimination of exogenous insulin use.

The two patients with at least 12 months of follow-up after VX-880 infusion, who were therefore evaluable for the study's primary efficacy endpoint, met the criteria for the primary endpoint of elimination of SHEs between Day 90 and Month 12 with an HbA1c <7.0%. The first patient achieved insulin independence at Day 270 through Month 24. This is a patient who has had T1D for nearly 42 years and prior to trial enrollment was on 34 units of daily exogenous insulin. The second patient achieved insulin independence at Day 180 through Month 12. This is a patient who has had T1D for 19 years and prior to trial enrollment was on 45.1 units of daily exogenous insulin. Starting at Month 15, this patient was started on four units of basal insulin daily, at the investigator's discretion. After the data cut-off date, a third patient achieved insulin independence at Day 180.

# Genetic Inhibition of *APOL1* Pore Forming Function Prevents *APOL1* Mediated Kidney Disease

JASN®
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

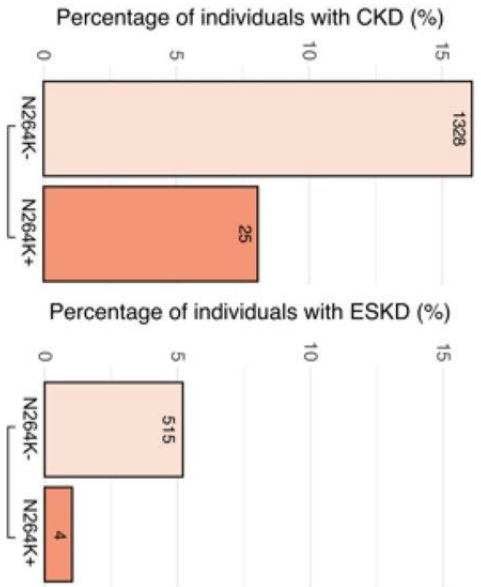
**Population:**
121,492 participants of African ancestry

**Biobank:**
Million Veteran Program
Vanderbilt BioVU
NIH All of Us

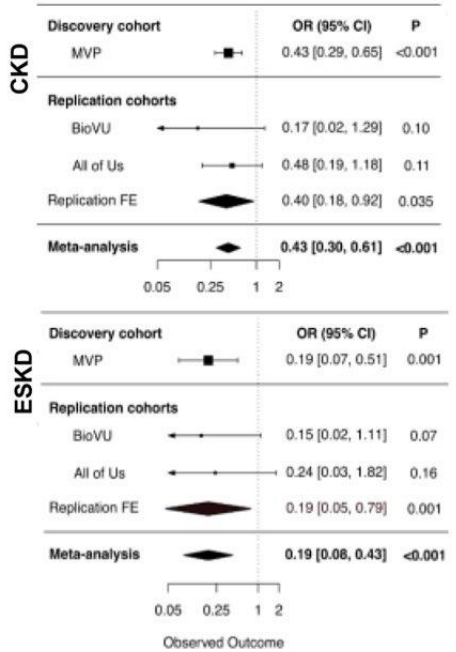
**Exposure:**
*APOL1* high-risk with or without the p.N264K variant

**Outcomes:**
Chronic Kidney Disease
End-stage kidney disease

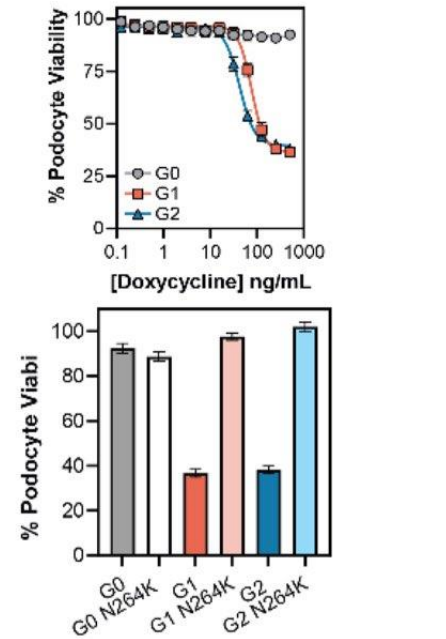
**Mechanistic Studies:**
Human immortalized podocytes and HEK cells




In MVP, *APOL1* high-risk without p.N264K was associated with increased CKD (OR 1.72; 95CI 1.60-.85) and ESKD (OR 3.94; 95CI 3.52-4.41).




In MVP, *APOL1* p.N264K mitigated the risk of *APOL1* high-risk in CKD (OR 0.43; 95CI 0.28-0.65) and ESKD (OR 0.19; 95CI 0.07-0.51) and in the replication.




In mechanistic studies of human immortalized podocytes, the cytotoxicity of *APOL1* G1 and G2 risk variants is attenuated by the N264K mutation.

**Conclusion:** *APOL1* p.N264K is associated with reduced risk of CKD and ESKD among carriers of *APOL1* high-risk variants to levels comparable to individuals with *APOL1* low-risk variants.

10.1681/ASN.0000000000000219

Source: https://journals.lww.com/jasn/fulltext/9900/genetic_inhibition_of_apol1_pore_forming_function.181.aspx

Article | Open Access | Published: 04 October 2023 **Nature**

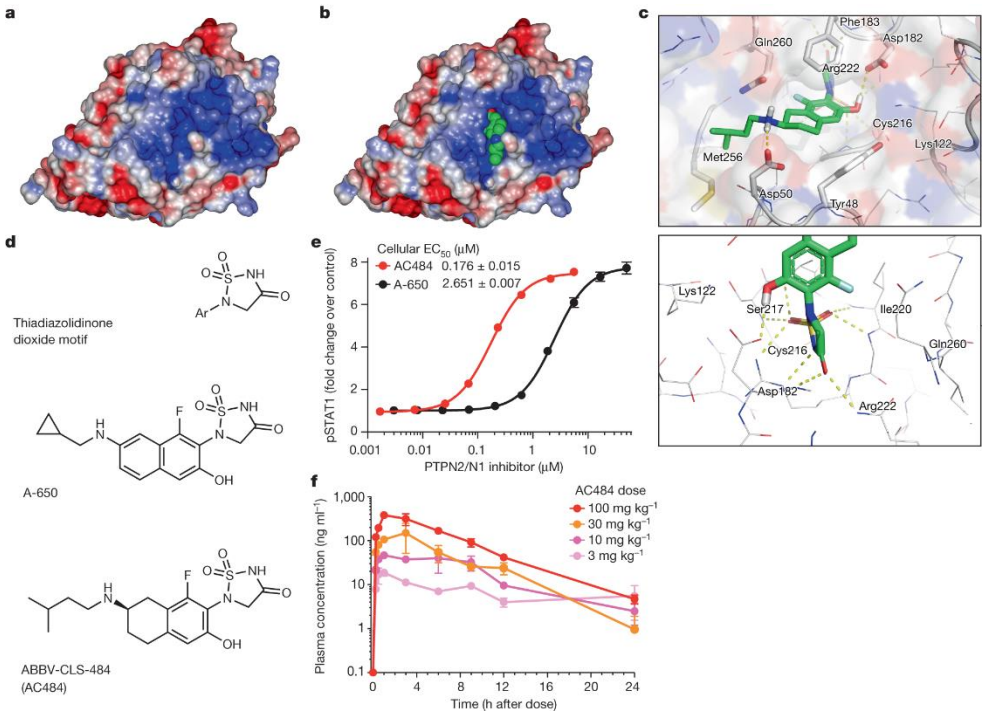
# The PTPN2/PTPN1 inhibitor ABBV-CLS-484 unleashes potent anti-tumour immunity

Christina K. Baumgartner, Hakimeh Ebrahimi-Nik, Arvin Iracheta-Vellve, Keith M. Hamel, Kira E. Olander, Thomas G. R. Davis, Kathleen A. McGuire, Geoff T. Halvorsen, Omar I. Avila, Chirag H. Patel, Sarah Y. Kim, Ashwin V. Kammula, Audrey J. Muscato, Kyle Halliwill, Prasanthi Geda, Kelly L. Klinge, Zhaoming Xiong, Ryan Duggan, Liang Mu, Mitchell D. Yeary, James C. Patti, Tyler M. Balon, Rebecca Mathew, Carey Backus, ... Robert T. Manguso + Show authors

Immune checkpoint blockade is effective for some patients with cancer, but most are refractory to current immunotherapies and new approaches are needed to overcome resistance. The protein tyrosine phosphatases PTPN2 and PTPN1 are central regulators of inflammation, and their genetic deletion in either tumour cells or immune cells promotes anti-tumour immunity3. However, phosphatases are challenging drug targets; in particular, the active site has been considered undruggable. Here we present the discovery and characterization of ABBV-CLS-484 (AC484), a first-in-class, orally bioavailable, potent PTPN2 and PTPN1 active-site inhibitor. AC484 treatment in vitro amplifies the response to interferon and promotes the activation and function of several immune cell subsets. In mouse models of cancer resistant to PD-1 blockade, AC484 monotherapy generates potent anti-tumour immunity. We show that AC484 inflames the tumour microenvironment and promotes natural killer cell and CD8+ T cell function by enhancing JAK–STAT signalling and reducing T cell dysfunction. Inhibitors of PTPN2 and PTPN1 offer a promising new strategy for cancer immunotherapy and are currently being evaluated in patients with advanced solid tumours.

Source: https://www.nature.com/articles/s41586-023-06575-7

## This promising asset is a result of collaboration between AbbVie and Calico.




**a**, Structure of PTPN2, with blue indicating the basicity of the active site (using a pH scale of 0–14, with pH < 7 indicating acidic (red) and pH > 7 basic (blue); pH 7 is neutral (white)). **b**, AC484 (green) in the PTPN2 protein, coloured as in **a**. **c**, Crystal structure of AC484 in the active site of PTPN2. **d**, Structure of PTPN2/N1 inhibitors, including AC484. **e**, Impact of PTPN2/N1 inhibitors on IFNγ-mediated STAT1 phosphorylation in B16 tumour cells ($n$ = 10 per inhibitor; mean ± s.e.m.). **f**, AC484 dose-escalating pharmacokinetics in mice at doses of 3, 10, 30 and 100 mg kg$^{-1}$ with once-daily dosing ($n$ = 3 per group; mean ± s.e.m.).

# Biosimilars Market

# Important Facts About the U.S. Biosimilars Market

**1 The largest piece of the biosimilar market (the U.S.) is effectively a branded market as sponsors have only rarely received labels for biosimilar interchangeability.**

Of course, contracting discussions with distributors and PBMs can be very important. There is more talk about interchangeability in the U.S. and Boehringer's recent move to introduce a biosimilar adalumab is an important one.

**2 Almost all the products on the market involve copies of one of the fifteen most widely sold biologic products.**

Of 357 biologics approved by FDA before 2010, only 12 have biosimilars on the market today. No product for any biologic that peaked at under $4bn in revenue

**3 A small number of players with large manufacturing operations dominate the U.S. biosimilars market today.**

Seven companies dominate the U.S. biosimilars market.

These are Amgen, Biogen, Celltrion, Coherus, Organon, Pfizer and Sandoz.

**4 While PBM's are blocking biosimilars, U.S. physicians in a buy-and-bill environment like the products.**

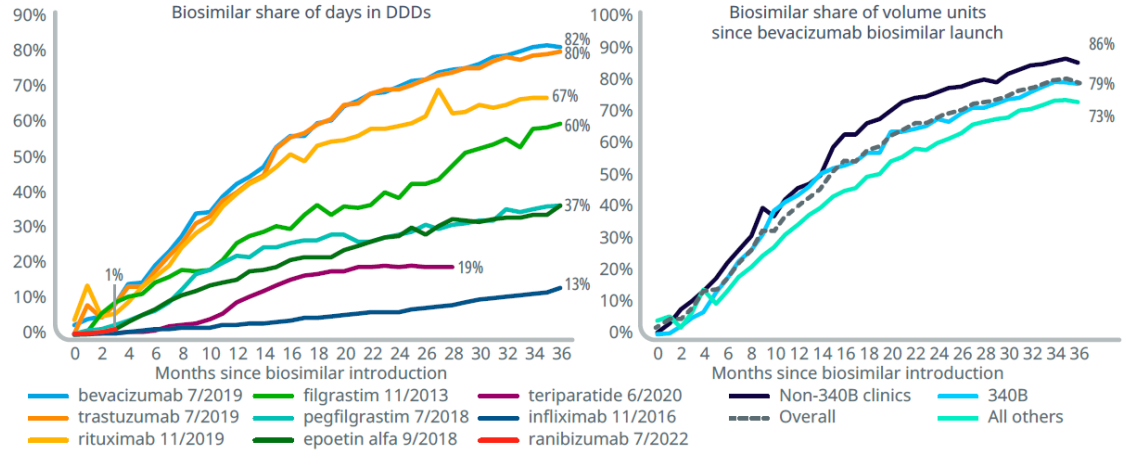
Recent IQVIA analysis shows that physician penetration in buy-and-bill environments is 55%. In contrast, the same analysis shows that PBM-mediated environments rarely use the drugs.

Importantly, physicians now get ASP+8% versus ASP+6% for branded biologics.

# Biosimilars Launches are Going Well

## Recent biosimilars have achieved high volume shares, reaching more than 60% within the first three years, varying by channel

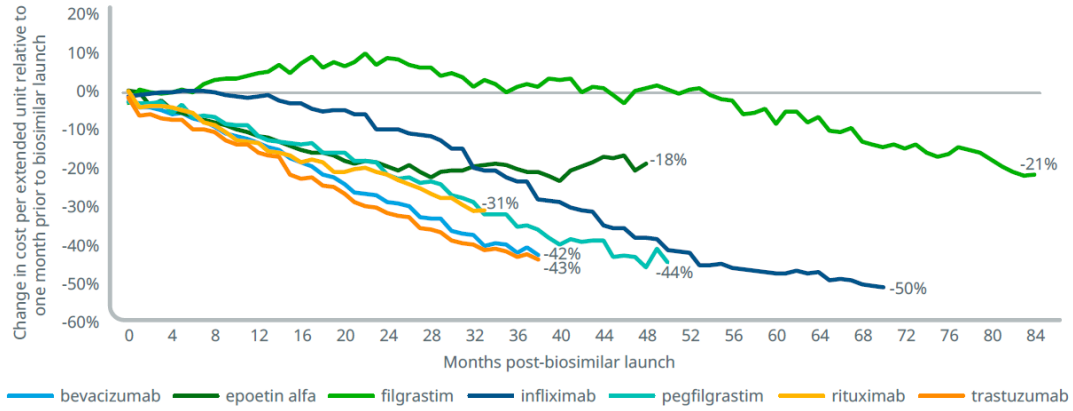
**Exhibit 9: Biosimilar share of volume since biosimilar launch**




Source: IQVIA MIDAS, IQVIA DDD, Oct 2022; IQVIA Institute, Dec 2022.

## Introduction of a biosimilar has driven down total molecule costs 18–50% with rate of decline driven by biosimilar uptake

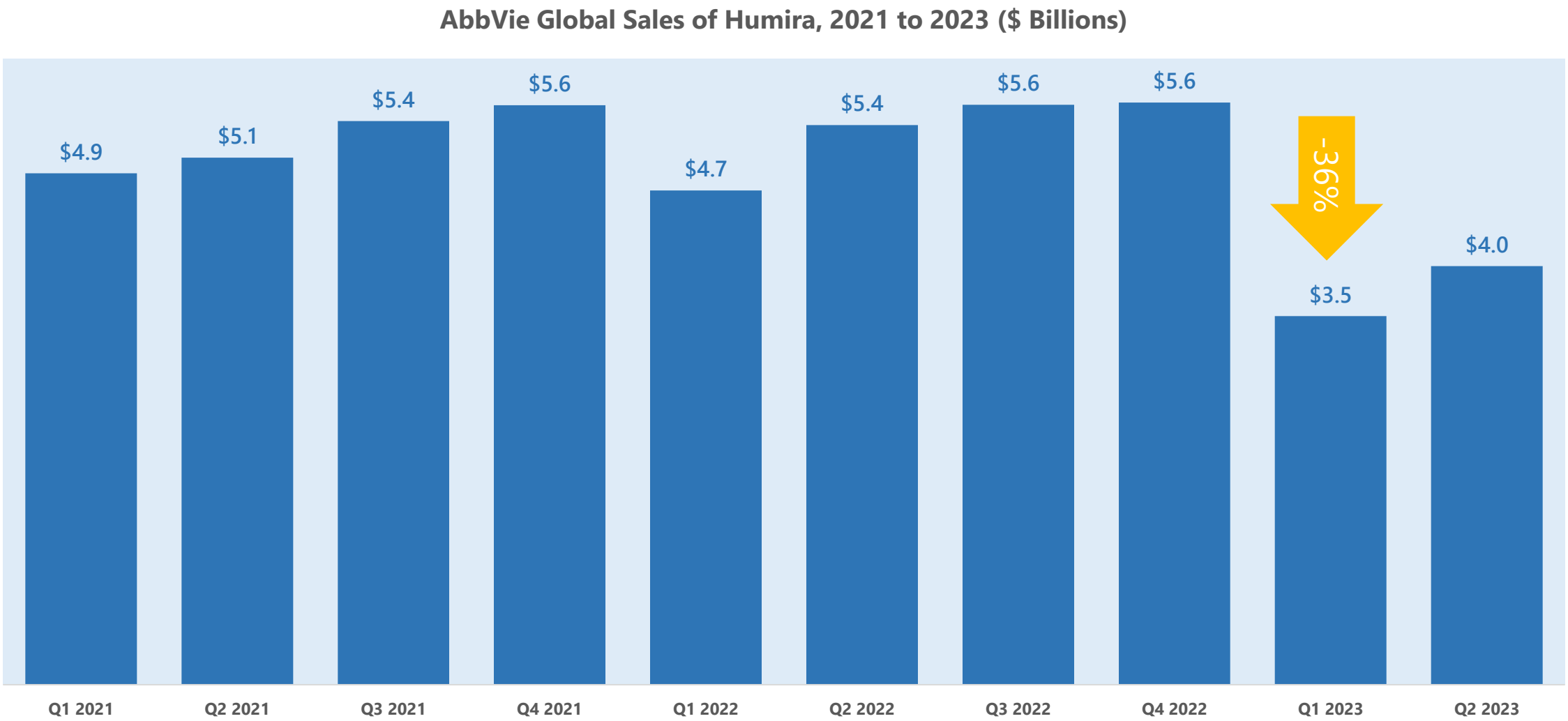
**Exhibit 17: Change in cost per extended unit following biosimilar launch relative to pre-expiry cost**




Source: IQVIA National Sales Perspective, US Market Access Strategy Consulting, Dec 2022.

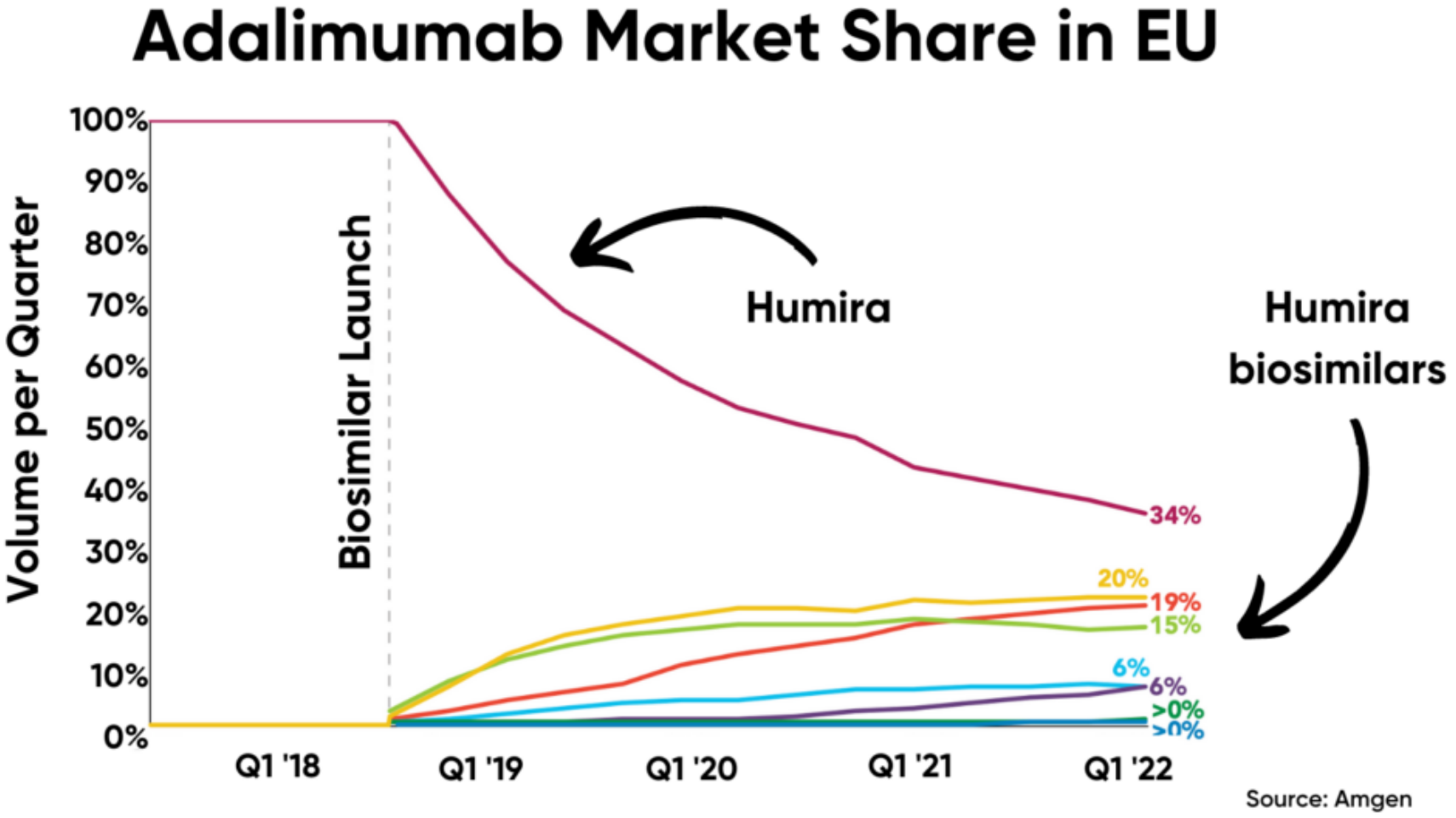
Source: IQVIA Institute.

# What Happened to Humira® Sales After Biosimilars Entered U.S. Market in 2023?




Source: AbbVie Press releases.

# Humira Europe Sales Dropped with Biosimilars Entry in 2019

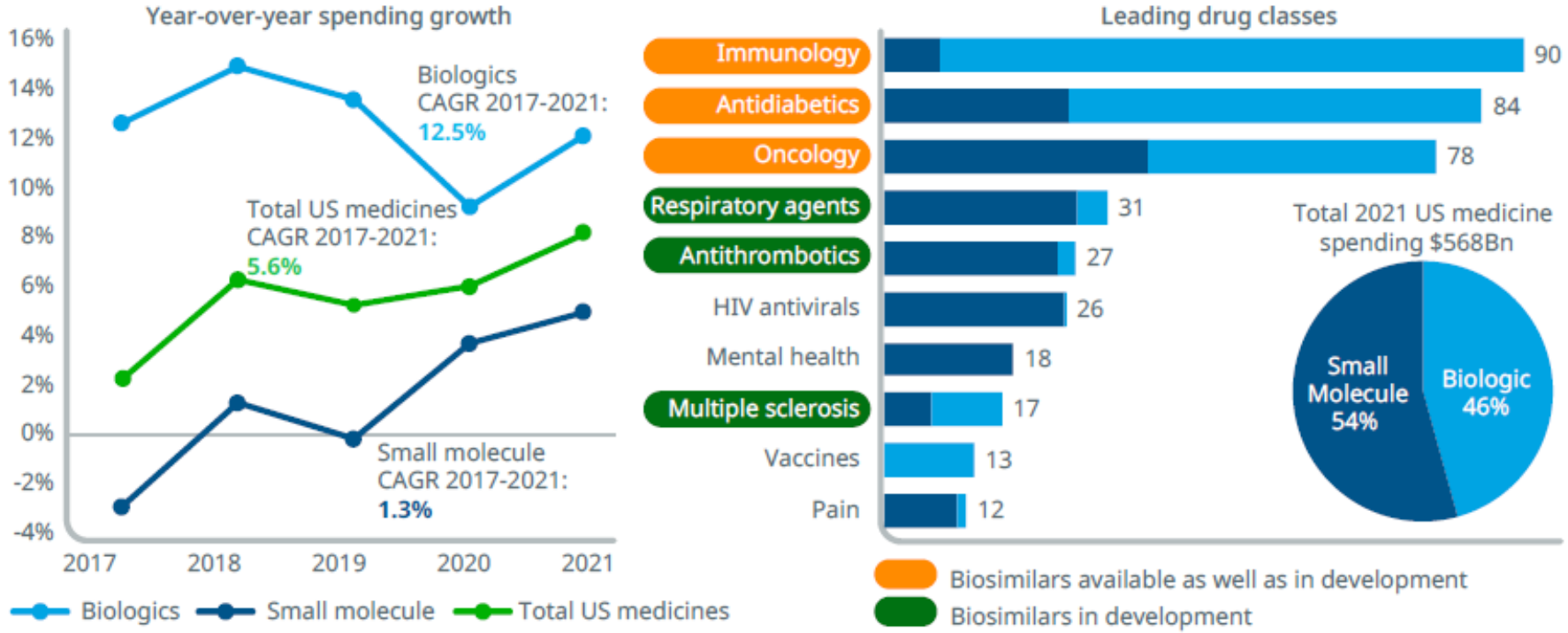



Source: https://workweek.com/2023/01/28/the-end-of-the-most-financially-successful-drug-in-history/

# Biologics Continue to Gain Share of U.S. Market

## The U.S. biologics market continues to grow faster than non-biologics on an invoice-basis, and now comprises 46% of spending

**Exhibit 1: Total U.S. invoice spending growth by type and leading therapy areas by 2021 spending, US$Bn**

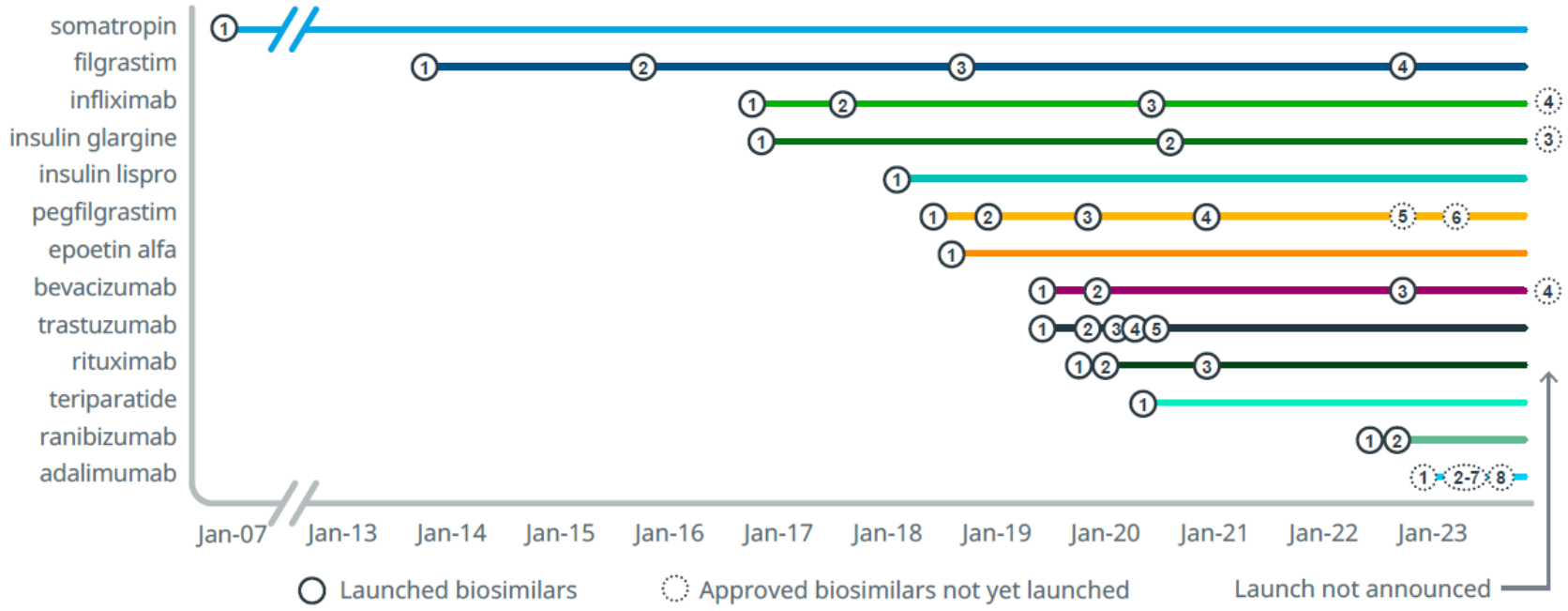



Source: IQVIA MIDAS, Dec 2021; IQVIA Institute, Nov 2022.

# By End of 2023 There Should be Around 40 Approved Biosimilars in the U.S.

**Since 2007, 30 biosimilars have launched in the U.S. with 10 more approved and set to launch by the end of 2023**

**Exhibit 5: Biosimilars approved and launched in the U.S.**




Source: IQVIA Institute, Dec 2022.

# FDA Trying to Make it Easier to Get Interchangeable Biosimilars Approved

## Sophia Humphreys, *AJMC*, August 2023

Biosimilars are cost-effective alternatives that are highly similar to originator/reference biologics in terms of efficacy and safety, yet the uptake of biosimilars in the United States has been gradual in part due to provider- and patient-related barriers.

To improve biosimilar uptake and adoption, the FDA has established an interchangeable designation for biosimilars. For FDA approval, a biosimilar must demonstrate that it is highly similar to the reference product and that there are no clinically meaningful differences between the reference biologic and the proposed biosimilar.

Interchangeable biosimilars are recommended to undergo additional studies to demonstrate that there is no change in efficacy or safety after 3 switches between the proposed interchangeable biosimilar and the reference product. Most states permit the substitution of a reference product for an interchangeable biosimilar without the approval of the prescribing physician.


Source: https://www.ajmc.com/view/understanding-interchangeable-biosimilars-at-the-federal-and-state-levels

# Boehringer Offers Interchangeable Biosimilar at 81% Discount to AbbVie's Humira

**Tristan Manalac, *Biospace*, October 3, 2023 (excerpt)**

Boehringer Ingelheim on Monday unveiled lower wholesale pricing for its adalimumab-adbm injection, the company's interchangeable biosimilar to AbbVie's blockbuster chronic inflammatory therapy Humira (adalimumab).

At its wholesale acquisition cost, adalimumab-adbm is now priced at an 81% discount to Humira. Boehringer Ingelheim also launched a branded version of the biosimilar in July 2023, bearing the brand name Cyltezo with a 5% discount versus Humira.

This "dual pricing approach" will help the adalimumab biosimilar contribute to the sustainability of the healthcare system, as well as "improve access to Adalimumab-adbm and help meet the varied needs of people with a variety of chronic inflammatory diseases," Stephen Pagnotta, executive director and biosimilar commercial lead at Boehringer Ingelheim, said in a statement.

According to adalimumab-adbm's label, its interchangeability designation indicates that there are "no clinically meaningful differences" between it and the reference product. This designation poses more stringent requirements—including demonstrating in trials that using the biosimilar in place of its branded counterpart does not compromise safety and efficacy—but also provides better prescribing flexibility. Interchangeable products may be used in place of the reference medicine without needing to change the prescription. First approved in 2002 for rheumatoid arthritis, Humira is a monoclonal antibody that binds to the TNF-alpha cytokine, a key player in the inflammatory cascade and driver of pathologic inflammation. The therapy has since been approved in several other indications, including Crohn's disease, ulcerative colitis, hidradenitis suppurativa and ankylosing spondylitis.

Humira has consistently been among AbbVie's best-selling assets. In 2021, the blockbuster therapy made more than $20.6 billion in total, representing over 14% growth compared to the prior year. However, its loss of exclusivity and the threat of biosimilar competition have eroded Humira's market footing and eaten away at its sales figures. In 2022, the antibody's revenues dropped by 22.2% in international markets. This downward trend in sales has only gotten worse this year. In the second quarter of 2023, Humira's total revenue was 25.5% lower than during the same period the previous year.

Aside from Boehringer Ingelheim, several other companies have also launched their Humira biosimilars. Leading the pack is Amgen, whose Amjevita hit the market in January 2023. Other offerings include those from Organon and partner Samsung Bioepis, Coherus Biosciences, Celltrion, and Sandoz.

Source: https://www.biospace.com/article/boehringer-challenges-abbvie-s-humira-with-interchangeable-biosimilar-at-81-percent-discount/

# Boehringer Ingelheim Explains Interchangeability



**An Interchangeable designation requires an additional study of multiple substitutions in patients** — an Interchangeability study. This study shows how patients do when they are switched back and forth from a reference product to the Interchangeable biosimilar. The Interchangeability study is designed to give providers confidence that patients can be switched with no increased risk in terms of safety or diminished efficacy, as compared to remaining on the reference product.

According to the FDA, prescribers and patients "can expect that the **Interchangeable product will have the same clinical result as the reference product in any given patient.**" And they "can be confident in the safety and effectiveness of an Interchangeable product, just as they would be for an FDA-approved reference product."

Source: https://www.boehringer-ingelheim.com/us/interchangeability/

# Much More Likely to See U.S. Biosimilar Adoption If and When Pharmacies Can Substitute

**Waterhouse DM, Ward P, Drosick DR, Burdette C, Davies D, Mendenhall MA. Sustainable Integration of US Food and Drug Administration-Approved Biosimilars: Pharmacy- Versus Physician-Driven Change. *JCO Oncol Pract*. 2023 Sep 22:OP2300309.**

**Purpose:** Biosimilars are clinically equivalent to branded products yet cost significantly less. Interchangeability is a US Food and Drug Administration (FDA) designation that allows generic drugs to be substituted for reference drugs at the pharmacy, without a physician's consent. Currently, no oncologic biosimilar has FDA approval for interchangeability.

**Methods:** Building on pharmacy auto-substitution processes with therapeutic interchange, Plan-Do-Study-Act methodology was used to automate conversions from reference biological products to Pharmacy and Therapeutics-/Physician-approved biosimilars. After establishing the baseline metrics, cycle 1 focused on full staff education (completed July 2020) with systematic pharmacy-driven biosimilar conversion initiated in September 2020 for rituximab, trastuzumab, and bevacizumab. Physician-initiated conversion of Neulasta biosimilar products was encouraged but not mandated. During cycle 2 (May 1, 2021-November 30, 2021), pharmacy-driven Neulasta biosimilar conversion was mandated. In cycle 3 (December 1, 2021-April 30, 2023), stakeholder education was reinforced and the sustainability of conversions was confirmed.

**Results:** Systematic pharmacy-driven conversion to biosimilar products improved over cycles 1 and 2 from baseline: 1.8% to 90.3% for rituximab, 9.2% to 89.7% for trastuzumab, and 20.5% to 96.1% for bevacizumab. Physician-driven biosimilar conversion for Neulasta was lower at 12.7% through April 2021. Pharmacy-driven Neulasta biosimilar conversion was initiated during cycle 2, resulting in a conversion rate of 39.7%. The conversion rates remained sustainable through April 2023.

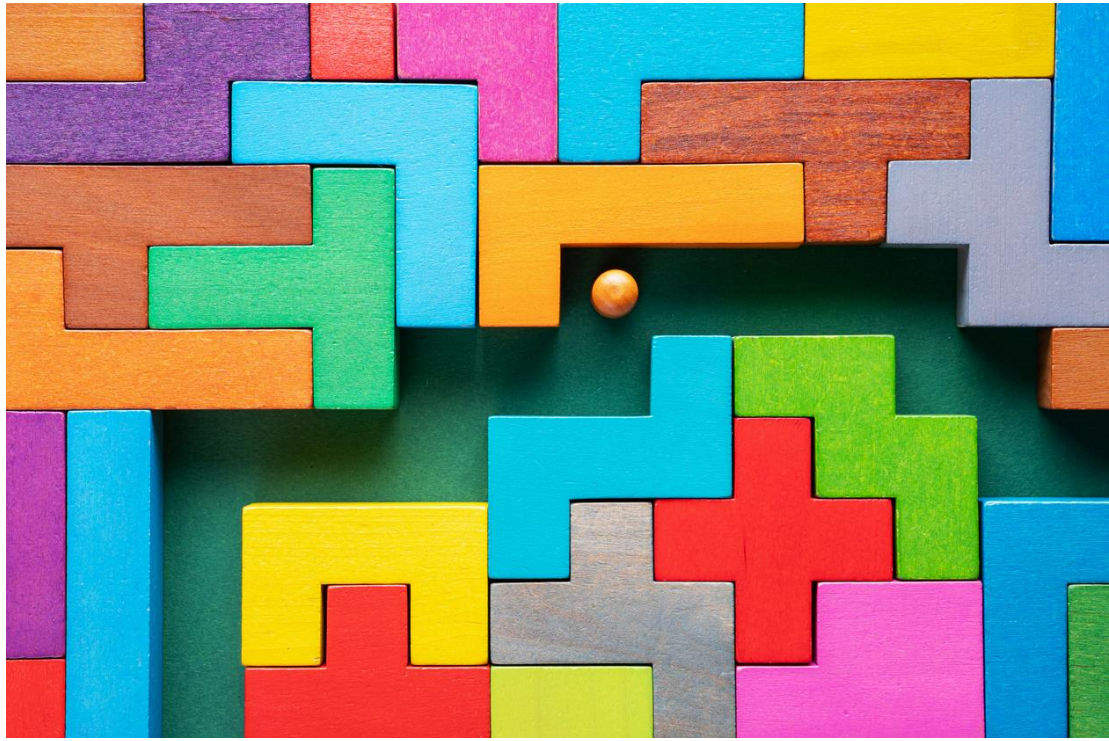
**Conclusion:** Pharmacy-driven auto-substitution of biosimilar products results in rapid and statistically significant biosimilar adoption. The pharmacy-based substitution approach was found to be far more effective than physician-driven substitution. Rapid conversion from branded products to FDA-approved biosimilar is feasible, measurable, and sustainable and can be scaled. Barriers to Neulasta conversion warrant further investigation.

Source: https://pubmed.ncbi.nlm.nih.gov/37738533/

# Game Theory: Interchangeability

- Very few sponsor's are willing to spend the extra money to get an interchangeable designation.
- If only one sponsor gets the designation, there will be very strong momentum for that sponsor's product because pharmacies can force the switch.
- PBM and distributor influence gets taken out of the system.
- If all sponsors go for interchangeability then there is no gain. But if no one else does then it can be highly attractive.

**This type of dynamic was called the "Prisoner's Dilemma" by the game theorist John Nash.**



# PLOS ONE Study Looks at Safety Events When Patients Switch To Biosimilars


**Herndon TM, Ausin C, Brahme NN, Schrieber SJ, Luo M, Andrada FC, Kim C, Sun W, Zhou L, Grosser S, Yim S, Ricci MS. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. *PLoS One*, Oct 3, 2023, 18(10):e0292231.**

Biosimilars are increasingly available for the treatment of many serious disorders, however some concerns persist about switching a patient to a biosimilar whose condition is stable while on the reference biologic. Randomized controlled studies and extension studies with a switch treatment period (STP) to or from a biosimilar and its reference biologic were identified from publicly available information maintained by the U.S. Food and Drug Administration (FDA). These findings were augmented with data from peer reviewed publications containing information not captured in FDA reviews. Forty-four STPs were identified from 31 unique studies for 21 different biosimilars. Data were extracted and synthesized following PRISMA guidelines. Meta-analysis was conducted to estimate the overall risk difference across studies. A total of 5,252 patients who were switched to or from a biosimilar and its reference biologic were identified. **Safety data including deaths, serious adverse events, and treatment discontinuation showed an overall risk difference (95% CI) of -0.00 (-0.00, 0.00), 0.00 (-0.01, 0.01), -0.00 (-0.01, 0.00) across STPs, respectively. Immunogenicity data showed similar incidence of anti-drug antibodies and neutralizing antibodies in patients within a STP who were switched to or from a biosimilar to its reference biologic and patients who were not switched.** Immune related adverse events such as anaphylaxis, hypersensitivity reactions, and injections site reactions were similar in switched and non-switched patients. This first systematic review using statistical methods to address the risk of switching patients between reference biologics and biosimilars finds no difference in the safety profiles or immunogenicity rates in patients who were switched and those who remained on a reference biologic or a biosimilar.

Source: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0292231

# Manufacturing Capabilities are Very Important

While generics cost between $1mm and $5mm to develop, biosimilars cost between $100mm and $200mm.

Biosimilars are more complex to develop and manufacture due to the inherent variability between one living cell and another, and the inability to exactly replicate the manufacturing or structure of the originator biologic

The FDA's complete response letters (CRLs) to big and small biosimilars players have been a key issues

Sandoz, Pfizer, Mylan, and Coherus have all received CRLs primarily for manufacturing-related issues, delaying the launch of biosimilar products

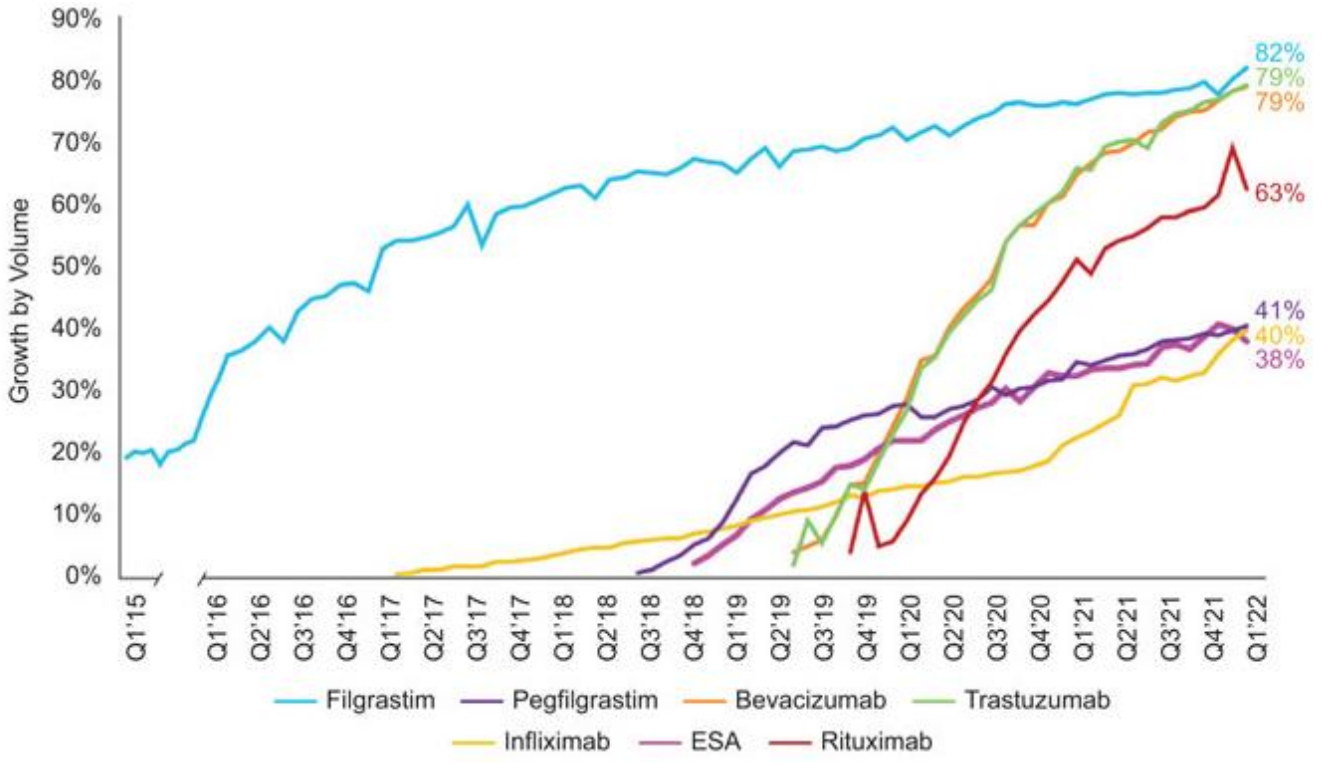
# European Biosimilar Market Adoption has been Strong and Growing

- Adoption of Remicade and Enbrel continues to increase in Europe
- Late entrants have slow adoption
- Scandinavia treats biosimilars as interchangeable drugs for new and existing patients in annual contracts
- Rituximab and trastuzumab biosimilar adoption has been strong and growing

Source: Bernstein Report. Chart from GABI Journal.

## Europe Market Overview

Biosimilars as Volume Share of the Reference Molecule Market




Biosimilars have done well in Europe but ensuing price competition has largely squeezed profits out of the market.

# Global Best Practices in Accelerating Biosimilar Adoption

**Alnaqbi et.al., "An international comparative analysis and roadmap to sustainable biosimilar markets," Front Pharmacol. 2023 Aug 24;14:1188368.**

TABLE 3 Examples of best practices in selected countries by key biosimilar policy area.

| Policy area | Best practice examples |
|---|---|
| Manufacturing and R&D | European Union legislation streamlines preparation for biosimilar entry prior to the loss of exclusivity, enabling rapid launch post patent-expiry |
| Regulatory approval | The United Kingdom Medicines and Healthcare products Regulatory Agency no longer requires clinical comparability studies for all products given latest research regarding their lack of additional value to regulatory assessments |
| Health technology assessment | Many countries like the Netherlands waive the need for biosimilar health technology assessment provided the indications included in the biosimilar label are the same as the originator |
| Pricing and reimbursement | In the Netherlands, biosimilars can launch at the same price as their originators, encouraging entry, then competition is used to promote cost savings. Moreover, pricing and reimbursement are applied as a single process, ensuring biosimilars' automatic reimbursement |
| Contracting | In the United Kingdom, long-term supply plurality is provided for adalimumab biosimilars, given that the market has been divided into 11 hospital groups. These groups are allocated a specific biosimilar or originator product, with degressive market shares for those products dependent on the competitiveness of the tender price they have offered |
| Biosimilar education and understanding | European educational campaigns spearheaded by the European Medicines Agency are often supplemented with national-level education in European countries, for example, at hospital/provider level to ensure holistic understanding of value across the country |
| Prescribing | In the United Kingdom, non-mandatory prescribing quotas still serve as an incentive for healthcare professionals. Moreover, gainsharing mechanisms implemented at some local Clinical Commissioning Groups have ensured that savings driven by biosimilars are reinvested in healthcare systems, improving their perception |
| Dispensing | In France, current dispensing policies do not undermine physicians' autonomy but instead promote shared decision-making also with pharmacists. Moreover, substitution policies do not interfere with robust tracing systems used for safety monitoring (i.e. 95% of retail pharmacies are connected to the traceability tool - the "dossier pharmaceutique" - even though not all of them use it systematically), and patients can have their voices heard without any misconceptions around biosimilar value being able to influence dispensing decisions |
| Monitoring | The United States has pharmacovigilance systems ensuring full transparency in monitoring, for example, by assigning a suffix to the biosimilar name in regulatory documents to distinguish between different biosimilars |

**Examples of key innovative changes to support greater biosimilar adoption include the UK's practice of not requiring clinical comparable studies, the Netherlands' practice of exempting biosimilars from HTA's and the dispensing practices of France.**

Source: https://pubmed.ncbi.nlm.nih.gov/37693908/

# IRA Drug Selection for Negotiation Sending Signal Regarding Biosimilars

**Joshua Cohen, Forbes, October 2, 2023 (excerpt)**

The Inflation Reduction Act isn't explicitly focused on curbing market entry impediments, but through actions taken by the Centers for Medicare and Medicaid Services–specifically, its selection of certain biologics for the initial round of price negotiation, such as Enbrel and Stelara–it appears to be indirectly entering the fray.

Biologics account for more than 40% of current prescription drug expenditures, while only representing 2% of all prescriptions. So on a per prescription basis, biosimilars–which have active ingredients similar to those of a previously licensed reference biologic–can yield substantial cost savings.

Manufacturers of the reference or originator biologics often build so-called patent thickets around their products to ward off competition from biosimilars. Due to biologics' complex structure and manufacturing processes, there are more patentable opportunities than small molecules drugs.

Extending monopolies has proven to be quite lucrative. Four blockbuster drugs—Humira, Avastin, Rituxan and Lantus—generated 56% of their overall revenue after expiration of their initial patents.

Among the drugs selected for Medicare price negotiation, the biologics Enbrel and Stelara are considered long monopoly products. When the Enbrel-referenced biosimilar Erelzi launches in 2029 it will have had to wait 13 years following its approval before entering the market. And a patient advocacy group suggested that the manufacturer of Stelara "makes an additional $18 million" in daily revenue by extending the product's market exclusivity.

With the selection of Enbrel and Stelara CMS appears to be sending a message to manufacturers with long monopolies to accelerate the path towards competition or else face potential price consequences.

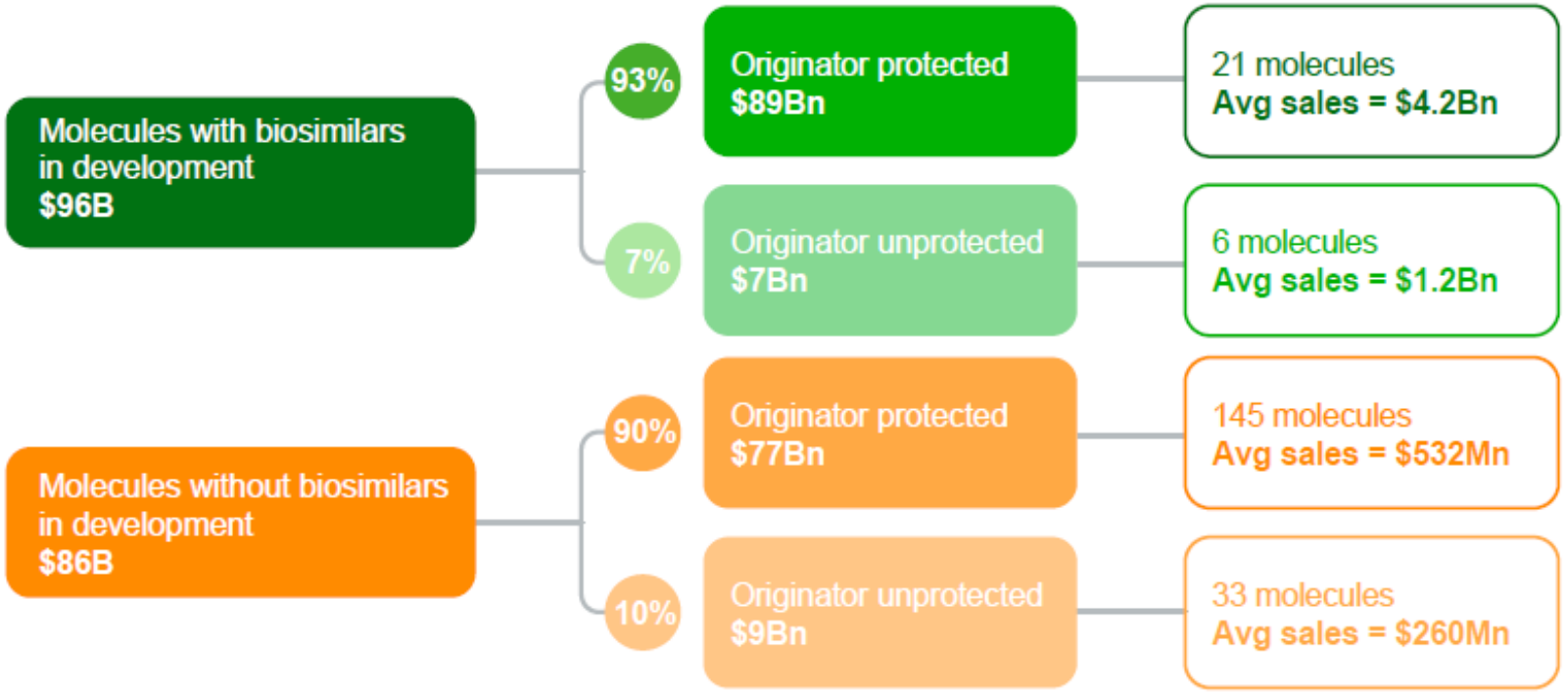
Patent thickets are among the reasons why biosimilars have so far had a much smaller impact in the U.S. than in Europe, where there is less expansive use of patent laws. European authorities have also approved more than twice as many biosimilars–93 in total–as the U.S. And, across most therapeutic classes in which biosimilars have been approved there has been more rapid and extensive biosimilar uptake.

Source: https://www.forbes.com/sites/joshuacohen/2023/10/02/inflation-reduction-act-may-curb-patent-practices-that-forestall-market-entry-of-biosimilars/

# Around 45% of the Biologics Market Does Not Have a Biosimilar in Development

## Most of the molecules with biosimilars in development continue to be protected, with only 7% unprotected

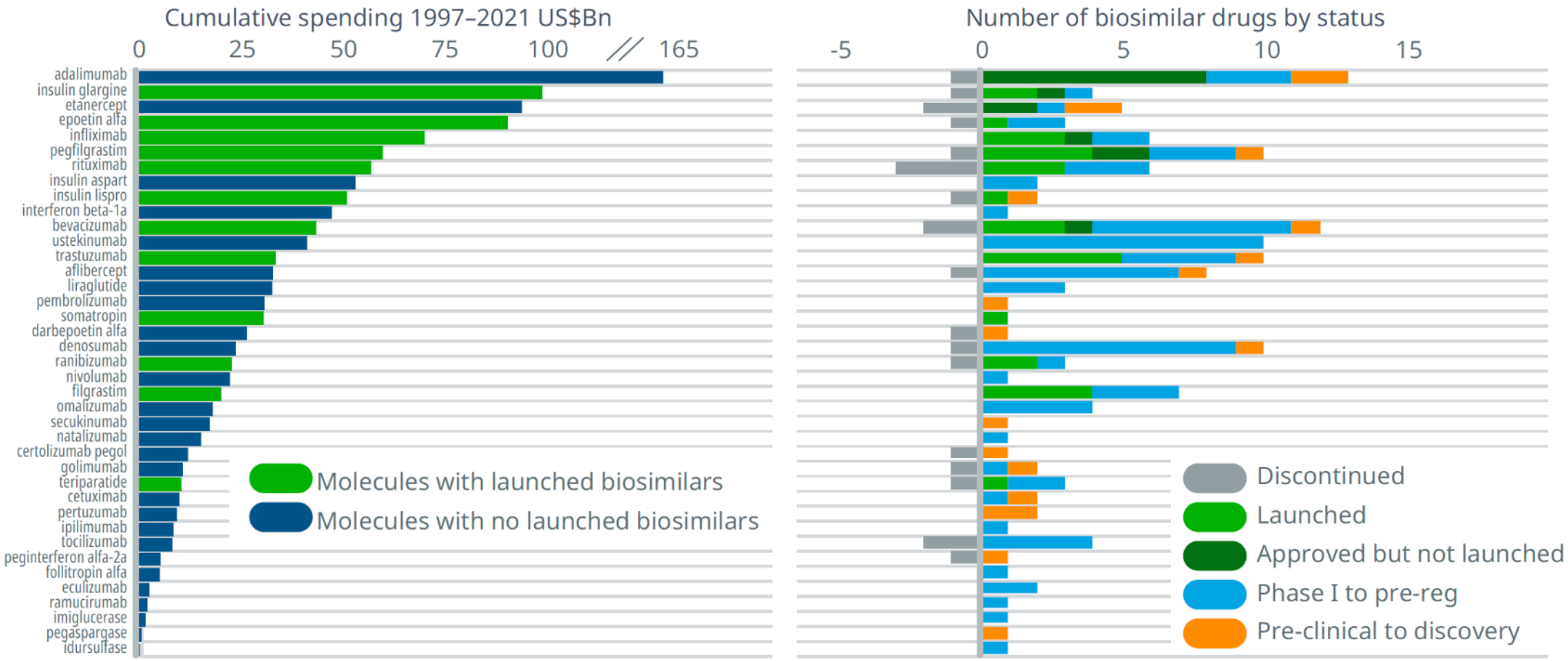
Exhibit 3: 2021 biologics market segmented by status of biosimilar development and market exclusivity




Source: IQVIA MIDAS, Dec 2021; IQVIA Pipeline Intelligence, IQVIA Institute, Nov 2022.

# Little Competition for Smaller Biologic Molecules

**Exhibit 6: Cumulative molecule spending and approved, launched and pipeline biosimilar products for the molecule**



# Disclosure

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