BofA SECURITIES

US Biopharmaceuticals

The 2024 US Biopharma Outlook

Industry Overview

Biopharma remains attractive with current backdrop

2023 was a roller coaster for the Biopharma industry with quality growth names continuing to win (Lilly, Vertex) but COVID / commercial execution stories falling flat (Pfizer, Moderna, Bristol). Indeed, despite having a strong year for new product approvals / launches and a big uptick in M&A/ licensing activities, both Pharma (DRG index: +5%) and Biotech (NBI index: +4%) underperformed the market (S&P500: +24%). Looking to 2024, we think valuation looks reasonable across Pharma (18X) and Biotech (14X) with the resurgence of M&A demonstrating a more proactive stance towards filling patent cliffs (i.e. LOEs). Importantly, given the current macro backdrop (uncertainty on the timing and magnitude of Fed rate cut) and what's likely to be higher HC policy noise but no real action, we are optimistic on the performance of Biopharma in 2024. To be sure, major innovation in very large therapeutic categories such as obesity, pain, and oncology is quite evident and should help orient generalist investors towards the sector. Among SMiD caps, we continue to expect volatility with a positive bias to names that have commercial products / phase 3 pipelines over pure platform technologies; this also likely the case when evaluating strategic attractiveness. Overall, we remain positive on the group in 2024 with a preference for higher growth names in Biopharma. **For more detailed stock-specific thoughts, see our accompanying report and join us TODAY at 10:30 am ET for our Biopharma outlook webinar.**

Where would we put money to work in 2024?

In large cap Biopharma, the sector continues to diverge into the 'haves' and the 'have-nots' based primarily on the strength of new product cycles. Indeed, we anticipate conversations around GLP-1 to continue unabated, with a heavy focus on Lilly's Mounjaro/ Zepbound launch trends as well as competitive/ non-incretin readouts. Nevertheless, Lilly is well-positioned to weather competitive threats with its breadth of portfolio, making it our top pick. Merck is another one of our favorites given its top-tier revenue growth profile (anchored by Keytruda/ Gardasil) at a reasonable multiple (12x vs. peer average 14x) and multiple launches/ catalysts (sotatercept, HER3-DXd, TROP2) this year. Importantly, management still has time to execute on BD to diversify Keytruda risk. For large-cap Biotech, Gilead is a favorite as we expect its HIV / Oncology portfolios to have another year of solid performance, with upside potential from Trodelvy uptake/ data readouts and improving sentiment on Gilead's overall Oncology strategy (Arcus and Arcellx collaboration). For SMid caps, we like the risk/reward of Amylyx going into TUDCA-ALS and PHOENIX readouts, with potential to be a top takeout target this year, and we like Neumora given the multiple shots on goal opportunities going into J&J's aticaprant readout in mid-24, KOSTAL-1 in 2H, and Cerevel's pivotal data in 2H, with potential to unlock significant opportunities in the neuropsych markets.

Favorite Large Cap Biopharmas: Eli Lilly (LLY) and Merck (MRK)
Favorite Biotechs: Gilead (GILD)
SMid Biotechs: Neumora (NMRA) and Amylyx (AMLX)
Least Favorites: Regeneron (REGN), Curevac (CVAC)

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Refer to important disclosures on page 84 to 87. Analyst Certification on page 82. Price Objective Basis/Risk on page 75.
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03 January 2024

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See abbreviation list, p. 71-74

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Portfolio Manager Review

Over the past few years, large cap Biopharmas have diverged into two categories - the "Haves" and the "Have Nots". The former group has a high impact, late-stage pipeline and / or recently launched products with significant peak revenue potential, while the latter group has a lower impact late-stage pipeline or newer launches that build momentum over a longer time period or meaningful LOEs. This is the framework we viewed the Biopharma space in 2022 and it is relevant in 2024 especially as higher impact new product launches gain momentum. Indeed, there's a strong correlation between a company's long-term growth and its valuation (multiple). Nearly all companies in the "have not" category have significant LOEs on the horizon where a pipeline is needed to fill the void (see Exhibits 1-4).

Exhibit 1: Strong correlation between LT revenue growth and valuation
LLY leads the pack on revenue growth and new launch revenue as % of total revenue

	'25-'30 Rev CAGR	2030 New Launch as % of Total Rev	P/E ('24)
LLY	13%	77%	47
BMRN	8%	49%	31
VRTX	7%	24%	25
REGN	4%	26%	20
BIIB	3%	38%	17
ABBV	3%	11%	14
JNJ	2%	33%	15
GILD	1%	34%	11
MRK	1%	25%	13
AMGN	1%	44%	14
PFE	-2%	42%	10
BMY	-5%	69%	7

Source: BofA Research, Bloomberg, VisibleAlpha

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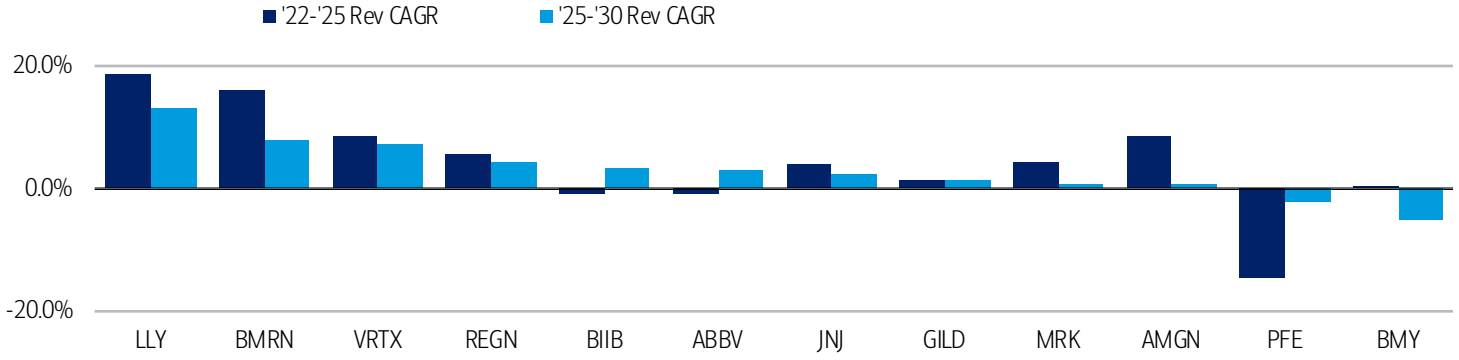
Exhibit 2: Large cap Biopharma Revenue growth
LLY leads the pack on revenue growth through the end of the decade.



Source: BofA Global Research, Visible Alpha

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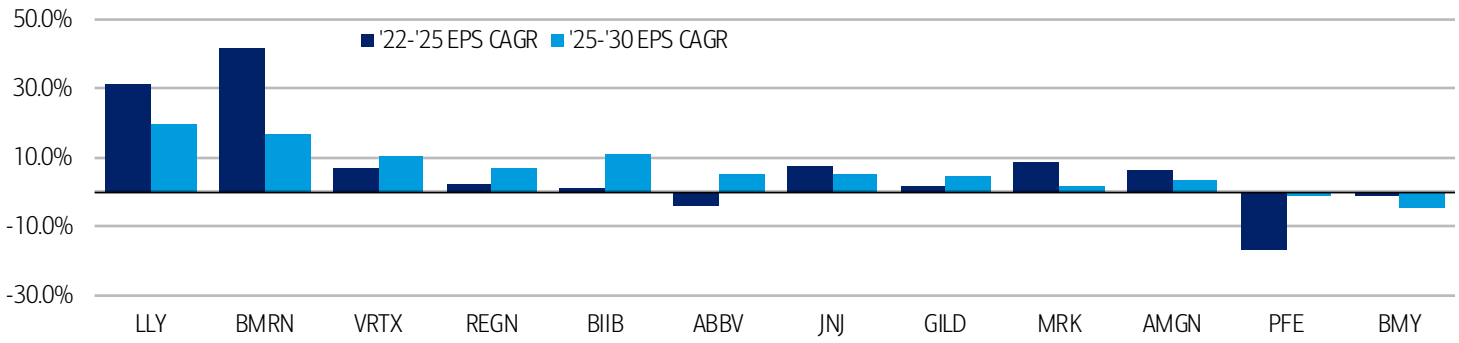
Exhibit 3: Large cap Biopharma EPS growth
LLY leads the pack on revenue growth through the end of the decade



Source: BofA Global Research, Visible Alpha

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Exhibit 4: Recent/ Potential Launches vs. Total Revenue
LLY leads the pack on new launches as % of company sales.

Company	2023	2024	2025	2026	2027	2028	2029	2030	Key products
ABBV	54,002	53,455	56,509	59,641	62,374	65,258	66,238	65,415	
New Launches	73	955	1,695	2,561	3,608	4,852	6,029	7,200	Epcoritamab, Navitoclax, Teliso-V, Cerevel, ImmunoGen
%	0%	2%	3%	4%	6%	7%	9%	11%	
AMGN	28,156	32,621	33,562	34,220	34,797	34,998	34,901	34,913	
New Launches	2,538	5,401	6,630	8,101	9,591	11,373	13,342	15,330	Lumakras, Tezspire, Tavneos, Rocatinlimab, AMG133, Olpasiran, Tarlatamab, Horizon
%	9%	17%	20%	24%	28%	32%	38%	44%	
BIIB	9,922	9,692	9,913	10,379	10,960	11,521	11,310	11,762	
New Launches	49	474	969	1,602	2,332	3,260	3,828	4,495	Leqembi, Skyclarys
%	0%	5%	10%	15%	21%	28%	34%	38%	
BMRN	2,413	2,835	3,284	3,754	4,212	4,587	4,832	4,844	
New Launches	464	806	1,196	1,577	1,927	2,244	2,378	2,359	Voxzogo, Roctavian
%	19%	28%	36%	42%	46%	49%	49%	49%	
BMY	44,766	46,034	46,539	45,728	45,328	40,781	37,394	35,625	Reblozyl, Zeposia, Breyanzi/Abecma, Sotyktu,
New Launches	3,572	5,833	8,627	11,629	15,008	18,347	21,724	24,587	Mava, Opdualag, Milvexian, Alunctamab,
%	8%	13%	19%	25%	33%	45%	58%	69%	Repotrectinib, Mirati, Karuna, Raze
GILD	27,091	27,644	28,332	29,000	29,932	31,988	31,942	30,503	
New Launches	1,441	3,094	3,173	4,591	7,515	12,253	16,074	10,518	Trodelvy, Tecartus, Lenacapavir, Zimberelimab
%	5%	11%	11%	16%	25%	38%	50%	34%	
JNJ Pharma	54,575	56,024	56,116	55,725	55,747	54,689	54,807	54,112	Carvykti, Rybrevant/lazertinib, Milvexian,
New Launches	866	2,036	3,883	6,352	9,342	11,917	14,949	17,918	Nipocalimab, Teclistamab, Talquetamab,
%	2%	4%	7%	11%	17%	22%	27%	33%	TARIS, JNJ-2113, aticaprant
LLY	33,739	39,191	47,854	57,194	67,464	76,468	82,959	88,596	Mounjaro/Zepbound, Orforglipron,
New Launches	5,303	11,890	20,237	29,411	40,578	51,716	60,658	68,220	Retatrutide, Pirtobrutinib, Retevmo,
%	16%	30%	42%	51%	60%	68%	73%	77%	Donanemab, Mirikizumab, Lebrikizumab
MRK	59,925	63,522	67,481	71,153	74,987	76,819	73,848	70,275	Vaxneuvance /V116, PCV, TIGIT, LAG3, TROP2
New Launches	880	1,587	3,141	5,411	8,035	11,020	14,334	17,264	ADC, Sotatercept, Daaichi ADCs, oral PCSK9,
%	1%	2%	5%	8%	11%	14%	19%	25%	TL1A, Belzutifan
PFE	58,692	61,306	62,389	61,840	60,785	58,262	56,302	55,579	Danuglipron, Etrasimod, Zavzpret,
New Launches	4,014	7,301	9,951	13,072	15,818	18,677	21,217	23,159	Erlanatamab, RSV, Litfulo, Marstacimab,
%	7%	12%	16%	21%	26%	32%	38%	42%	Vepdegestrant
REGN	12,936	13,582	14,359	15,099	16,111	16,928	17,292	17,659	
New Launches	851	1,181	1,679	2,122	2,731	3,412	4,043	4,530	Libtayo, Odronextamab, Itepekimab,
%	7%	9%	12%	14%	17%	20%	23%	26%	Fianlimab, Linvoseltamab
VRTX	9,867	10,550	11,469	12,402	13,310	14,255	15,314	16,348	
New Launches	0	219	629	1,154	1,795	2,370	3,182	3,963	Exa-cel, VX-864, VX-880, VX-548

Exhibit 4: Recent/ Potential Launches vs. Total Revenue
LLY leads the pack on new launches as % of company sales.

Company	2023	2024	2025	2026	2027	2028	2029	2030	Key products
%	0%	2%	5%	9%	13%	17%	21%	24%	

Source: BofA Global Research, VisibleAlpha

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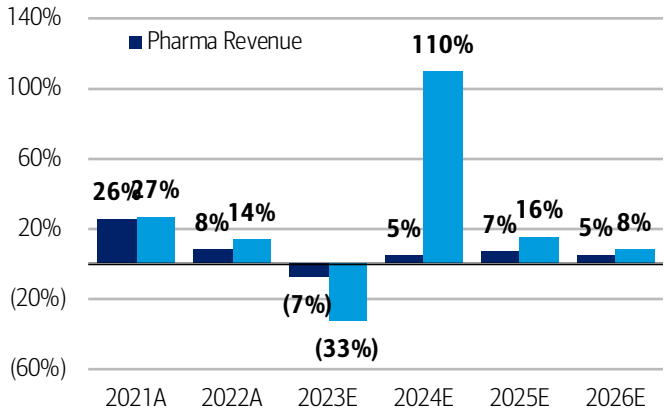
We saw growth from exciting new product cycles, but meaningful LOE's either occurring, or on the horizon, muted expectations for both top- and bottom-line growth. For both Pharma and Large Biotech, 2024-2026 is a period where growth (revenue and EPS) accelerates meaningfully as LOEs moderate, or the COVID-19 headwinds abate, before the next major LOEs come into full effect.

Exhibit 5: Major US Pharma Rev./EPS Expected Annual Growth Rates
Large M&A/licensing deals in 2023 affecting the growth rates



Source: Bloomberg, Companies include Pfizer, AbbVie, Merck, Lilly, Bristol, J&J

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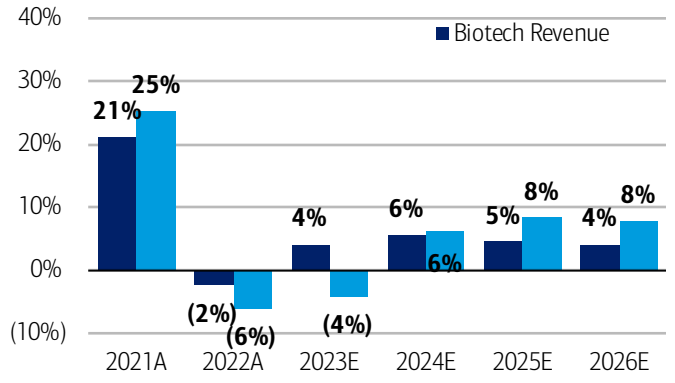
Exhibit 6: Large Cap Biotech Rev./EPS Expected Annual Growth Rates
Large M&A/licensing deals in 2023 affecting the growth rates



Source: Bloomberg: Companies include Amgen, Biogen, Gilead, Regeneron, Vertex

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In terms of new product cycle, we think 2024 will be a slower year than 2023 as biopharma companies focus on commercial execution ahead of major LOE overhangs mid-decade. Overall, we'd characterize markets for the new drug approvals in 2024 as smaller (e.g., myelofibrosis, 3L+ SCLC) or less exciting as the products are entering a crowded market with similar therapeutic options already available (e.g., odronextamab, linvoseltamab, Moderna's RSV vaccine). We think Karuna's (Bristol) KarXT is one of the more exciting approvals and launches in 2024 as it would be a first-in-class drug with label expansion opportunities, and Merck's sotatercept for the treatment of PAH, which our KOL's have described as treatment paradigm-changing.

Below we highlight product launches, approvals, and label expansion updates in 2024:

Exhibit 7: 2024 product launches, approvals and label expansion updates
In terms of new product cycle, we think 2024 will be a slower year than 2023 as biopharma companies focus on commercial execution.

Product	Indication	MOA / Target	Company	Est. Launch Timing
		New Drug Launches		
litfulo	vitiligo	JAK / TEC	Pfizer	YE23/1Q24
velsipity	ulcerative colitis	S1P	Pfizer	YE23/1Q24
Zepbound	obesity	GLP-1 / GIP	Eli Lilly	YE23/1Q24
Omvoh	ulcerative colitis	IL-23	Eli Lilly	YE23/1Q24
Abrysvo	maternal RSV vaccine	RSV vaccine	Pfizer	YE23/1Q24
Casgevy	sickle cell disease	gene therapy	Vertex / CRISPR	1H24
lebrikizumab	atopic dermatitis	IL-14	Eli Lilly	1H24
sotatercept	Pulmonary arterial hypertension (PAH)	BMPR-II	Merck	1H24
donanemab	Alzheimer's disease	amyloid-beta	Eli Lilly	1H24
tarlatamab	Small cell lung cancer (SCLC)	DLL3	Amgen	2H24
ABBV-951	advanced Parkinson's Diseases	dopamine replacement	AbbVie	2H24

Exhibit 7: 2024 product launches, approvals and label expansion updates
In terms of new product cycle, we think 2024 will be a slower year than 2023 as biopharma companies focus on commercial execution.

Product	Indication	MOA / Target	Company	Est. Launch Timing
RSV vaccine	maternal / pediatric RSV	RSV vaccine	Moderna	2H24
odronextamab	r/r diffuse large B-cell lymphoma (DLBCL)	CD20 / CD3	Regeneorn	2H24
linvoseltamab	r/r multiple myeloma	BCMA	Regeneron	2H24
HER3-DXd	EGFR 2L+ NSCLC	HER3	Merck/ Daiichi	2H24
Rybrevant/lazertinib	EGFR NSCLC 1L and 2L+ NSCLC	EGFR / MET	Johnson & Johnson	2H24
KarXT	schizophrenia	M4 PAM	Karuna (Bristol)	4Q24
		New Drug Approvals		
donanemab	Alzheimer's disease	Amyloid-beta	Eli Lilly	1Q24
sotatercept	Pulmonary arterial hypertension (PAH)	BMPR-II	Merck	March 2024
RSV vaccine	maternal / pediatric RSV	RSV vaccine	Moderna	1H24
odronextamab	r/r diffuse large B-cell lymphoma (DLBCL)	CD20 / CD3	Regeneorn	1H24
linvoseltamab	r/r multiple myeloma	BCMA	Regeneron	mid-2024
KarXT	schizophrenia	M4 PAM	Karuna / Bristol	Sept 26, 2024
ABBV-951	advanced Parkinson's Diseases	dopamine replacement	AbbVie	2H24
Rybrevant/lazertinib	EGFR NSCLC 1L and 2L+ NSCLC	EGFR / MET	Johnson & Johnson	2H24
HER3-DXd	EGFR 2L+ NSCLC	HER3	Merck/ Daiichi	June 26, 2024
tarlatamab	3L+ small cell lung cancer	DLL3	Amgen	Jun 12, 2024
tavapadon	Parkinson's disease	D1 / D4 partial agaonist	Cerevel (AbbVie)	2024
navitoclax	myelofibrosis	BCL-XL	AbbVie	2024
SubQ Opdivo	multiple solid tumors	PD-L1	Bristol	2024
		Label Expansion		
Skyrizi	Ulcerative Colitis	IL-23	AbbVie	1Q24
Epkinly	r/r follicular lymphoma	CD20 / CD3	AbbVie	2024
Elahere	FRα platinum sensitive ovarian cancer	FRα	ImmunoGen (AbbVie)	YE24
Dupixent	Type 2 chronic obstructive pulmonary disease (COPD)	IL-4 / IL-13	Regeneron	mid-2024
Tremfya	Ulcerative Colitis	IL-23	J&J	YE24
Botox	platysma and masseter aesthetics	botulinum neurotoxin	AbbVie	2024
Verzenio	castrate-resistant prostate cancer	CDK 4/6	Eli Lilly	2024

Source: Company reports, BofA Global Research

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2023 – A Quick Review

Biopharma as a whole underperformed the broader market, with a slight preference for SMids (over Large Cap) while investors preferred the overall healthcare space over biopharma (given the risk on trade). Despite the underperformance a lot of things went right in the sector, including high-profile readouts (e.g., Novo's/Lilly's Select, Lilly's Trailblazer-ALZ 2), successful launches (e.g., Lilly's Mounjaro) and regulatory approvals, signaling a more predictive regulatory landscape. Indeed, we'd argue that changing risk appetites were likely at the crux of Pharma underperformance, following years of broader market outperformance as investors sought defensive positioning in an uncertain macro environment. Further, companies that offered differentiated growth assets, like Lilly and Vertex were shielded from sector weakness and performed well in 2023. M&A also remained top of mind throughout 2023 given the 1) low SMid cap valuations, 2) meaningful LOE revenue holes in the back half of the decade, and 3) the significant capital Pharma/ Large Biotech could deploy. Indeed, M&A spend recovered well y/y in 2023 as companies paid higher premiums for quality assets.

As we anticipated in last year's outlook, high quality growth names (the "Haves") such as Eli Lilly (+59%) and Vertex (+41%) outperformed while the poor commercial performers/ COVID (the "Have Nots") underwhelmed (Bristol, Pfizer, Moderna). Given the macro backdrop (soft vs hard landing and timing/ magnitude of potential rate cuts), biopharma's relative attractive valuation, and resurgence of M&A/ licensing activities, Generalists may become interested in the sector again, following the Tech sector outperformance in 2023. Indeed, in our view, investors will continue to reward quality, growth stocks and remain cautious on value names with limited clarity on long-term outlook. Regardless, we expect BioPharma to continue the rally from late 2023 through early 2024, until there's a clear path towards the economic "soft landing" scenario. On SMid caps, we expect volatility to continue, but there will likely be a positive bias to

names which have commercial products / phase 3 pipelines over pure platform technologies.

Exhibit 8: Historical Performance Tracker for Biotech and Pharma vs. the S&P 500
Biopharma underperformed the broader market in 2022, with Pharma meaningfully outpacing Biotech

Returns	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
NBI	32%	66%	34%	11%	-22%	21%	-9%	24%	26%	-1%	-11%	+6%
DRG	11%	27%	14%	2%	-11%	13%	4%	15%	5%	20%	+5%	+4%
S&P 500	13%	30%	11%	-1%	10%	19%	-6%	29%	16%	27%	-19%	+25%
Relative Difference	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**
NBI	19%	36%	23%	12%	-31%	2%	-3%	-4%	12%	-28%	+8%	-19%
DRG	-2%	-3%	2%	2%	-21%	-6%	11%	-14%	-11%	-7%	+24%	-21%

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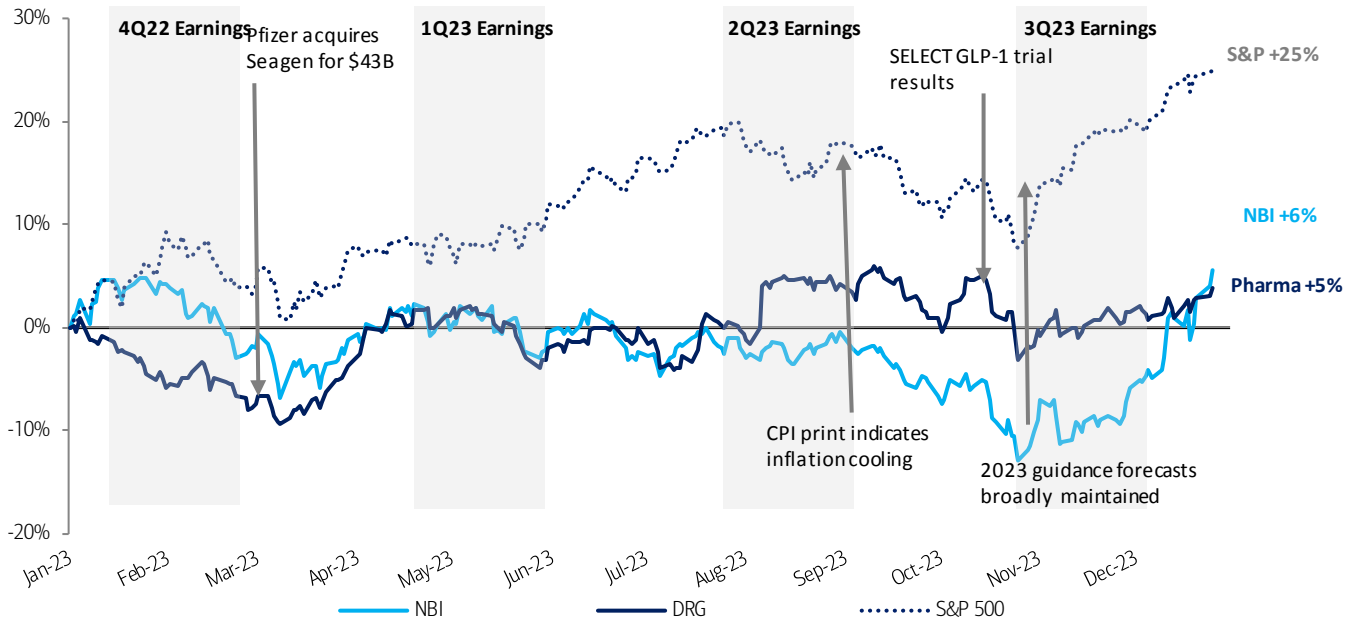
Looking to the start of 2023, we expected growth to be biased to growthier pharma over defensive names, in large part due to increasing risk appetites, innovative new product cycles, and notable study readouts. We would say this thesis played out, with 1) solid launches in diabetes/obesity justifying investor excitement in the space, and 2) high profile readouts in ADCs and pain bringing interest to the space. That said, high rates and limited transformational M&A / a lack of substantial IPO activity weighed on SMid cap performance for better part of the year, but sentiment has picked up in Q4 with a more acute focus on binary events and catalysts trending more positive. We'd also note that the lack of regulatory predictability was also weighing on the space until late 3Q, when Amgen and FTC settled the dispute with the closing of Horizon deal thereafter. As such, we'd say the regulatory landscape has gotten more predictable as of late and we anticipate M&A/ licensing activities to remain unabated in 2024.

Exhibit 9: NBI index and DRG index vs. S&P 500, FY2023 Performance
The NBI (Biotech) and DRG (Pharma) indices both underperformed the S&P 500



Source: BofA Global Research, Bloomberg, company reports

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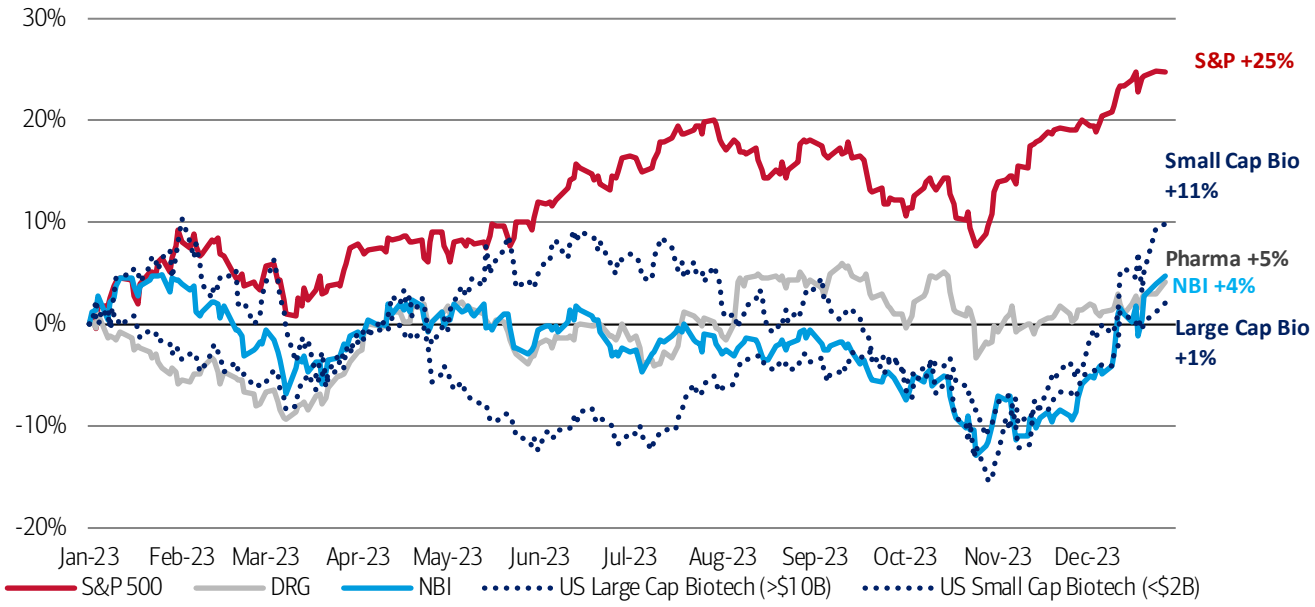
Looking ahead to 2024, we remain positive on the sector for a host of reasons. We believe this year's back half run in shares is indicative of growth appetites for the space as valuations remain reasonable. Moreover, a string of deals through the back half of year highlight growing interest in innovative technologies (ADC, radiopharma) and challenging neuropsych space (schizophrenia, MDD), indicative of the risk-on/ "whatever it takes" approach that the large cap BioPharma is employing in order to tackle LOE headwinds, which could not only keep investors engaged, but also lead to more ground-breaking development in areas of high unmet need. That said, we do acknowledge that the sector is facing significant LOE's (e.g., Merck's Keytruda in 2028), however biosimilar AbbVie's Humira uptake has been slower than expected in 2023 and we've seen companies accelerate innovation to overcome these hurdles, which keeps us positive on the sector. We think fast-tracking innovation and an emphasizing execution are key to engaging investors both on the Pharma and SMid cap level. Indeed, in our view, 2023 was another year of accelerated innovation (e.g., gene editing/ therapy, ADCs in difficult to treat cancers, non-opioid pain drugs) and we expect the pace to continue looking to 2024.

Exhibit 10: Price performance for the Biopharma sector (broken out by category) in 2023
Both pharma and large cap biotech underperformed, driven in large part due to the risk-on trade



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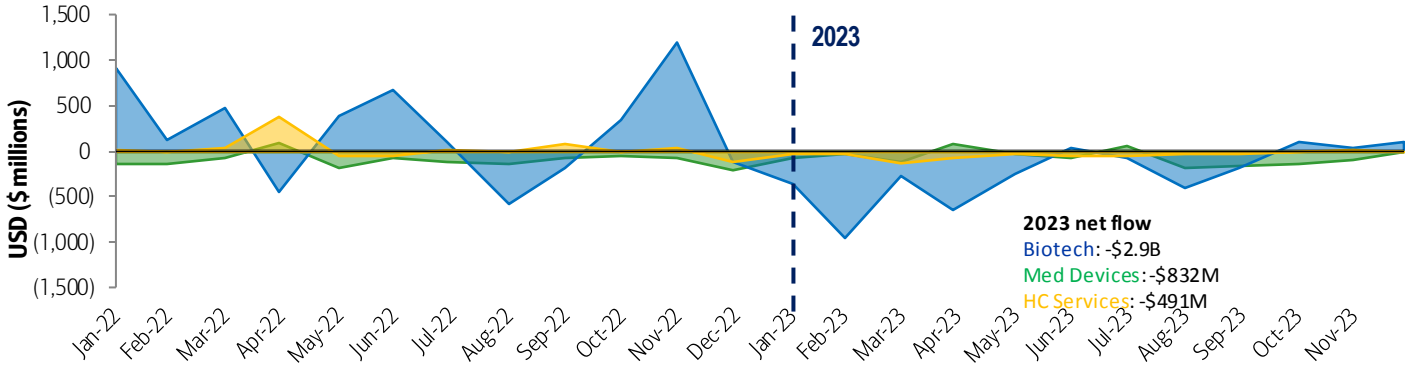
Biotech Fund Flows and Active Manager Positioning Positive into YE

2023 Biotech fund flows were generally more consistent than 2022, as investors cut biotech positions throughout the year (see exhibit **11**). The Biotech sector as a whole **ended the year with a net outflow of $-2.9B**, largely driven by large outflow in the first half of the year. We were not surprised to see such a large magnitude of outflows for Biotech in 1Q as this coincides with underperformance of commercial Biotech names which saw significant downward pressure on share price.

In Exhibit 11 below, we capture the monthly inflows and outflows across the major Biotech, Medical devices, and Healthcare services funds. **Biotech ended up being the worst performer in 2023** between the three categories, with more than $-2.9B in net outflows - though as we noted with much less fluctuation vs. what we saw back in 2022. Medical Devices continued to struggle for a second year, with a net outflow of -$832M in 2023 following a net outflow of -$1.1B in 2022. Healthcare Services also had poor results this year with an estimated -$491M outflow in comparison to a net inflow of +362M seen in 2022.

There were **more periods with net outflows vs. outflows** in 2023 for the Biotech sector (8 months with net outflows vs. 4 months with net inflows), driving the net negative outflows for the sector. Indeed, there were multiple months with -$300M-$900M in monthly outflows, while no month had >$100M in net inflows. Taking it a step further, when looking at the breakdown between the IBB index (iShares Biotechnology ETF) and the XBI index (SPDR S&P Biotech ETF), it appears there is an even distribution of fund flows. The collective net outflows in Exhibit 11 were almost perfect split between the XBI, which had +$-1.3B outflows whereas the IBB had outflows of +$-1.4B for the year (First Trust Connections NYSE Biotechnology, FBT, had a new outflow of -$216M).

Exhibit 11: Monthly ETF Fund Flows Across Biotech, Medical Devices, and Healthcare Services (2023 vs. 2022)
Biotech fund flows ended the year with -$2.9B in net inflows, largely driven by a weak first half of the year



Source: BofA Global Research, Bloomberg; Biotech includes XBI, IBB, and FBT; Medical Devices includes IXI and XHE; Healthcare Services includes IHF

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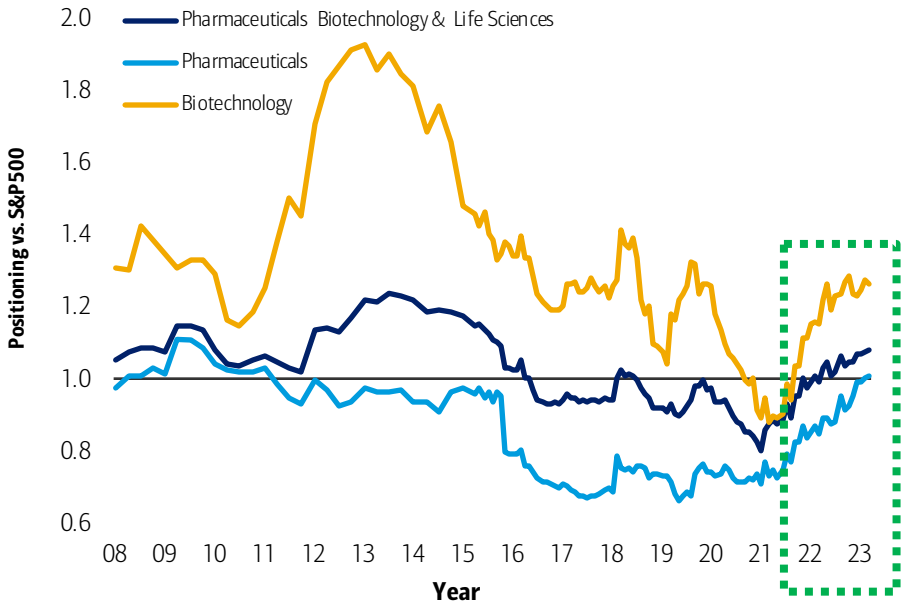
The interest of active managers in Biotech and Pharma has also been accelerating since reaching lows in 2021. In Exhibit 12, we highlight the positioning in Pharma and Biotech stocks compared to the weighting of those sectors in the S&P500 index where >1.0 is overweight and <1.0 is underweight versus the index. Indeed, money managers are now overweight in Biotech and at weight with Pharma. We think this makes sense as the broad sector faces headwinds but select names have been able to outperform. **Looking to 2024**, we expect this trend to continue as active money managers adopt a "stock picker" mentality versus passively investing in the sector as a whole. Based on historical numbers, we argue there is still room for money managers to increase their positioning in both Biotech and Pharma which should continue to drive the outperformance we saw late in the year. That said, we continue to anticipate net inflows into Biotech funds as upcoming catalysts and growing demand in obesity engage generalist investors in the space.

Exhibit 12: Active manager positioning data for Biotechnology and Pharmaceuticals relative to S&P500
Positioning is slightly overweight relative to historical trends in 2023



Source: BofA Global Research, Lipper, LionShares

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Healthcare Performance Drivers

Health Care (HC) had a respectable 2023 but came in the bottom third of S&P500 Global Industry Classification (GICS) sectors for relative annual growth (see Exhibit 13), below previous years. We attribute this to the risk on attitude of markets in 2023, in addition to high interest rates and increasing legislative risk as the IRA brings drug pricing reform into focus. We suspect Health Care will trade higher as the focus pivots to new launches/ product cycles in 2024. Indeed, we are optimistic on the sector as a whole and argue growth-oriented healthcare names should continue to outperform in 2024 as the macro environment improves.

Exhibit 13: S&P 500 Performance by Sector: Relative Annual Performance
Health Care was a bottom 3rd performer in 2023

S&P 500 Performance by Sector: Relative Annual Growth													
Rank	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
1	UTL	HC	DIS	TEC	DIS	STA	IND	REA	IND	IND	STA	ENR	COM
2	ENR	DIS	IND	UTL	IND	COM	HC	UTL	COM	DIS	TEC	UTL	TEC
3	IND	TEC	MAT	IND	REA	MAT	DIS	DIS	FIN	COM	IND	STA	DIS
4	TEC	IND	HC	REA	ENR	UTL	FIN	IND	ENR	HC	FIN	IND	IND
5	DIS	REA	REA	HC	TEC	REA	REA	TEC	DIS	REA	HC	HC	FIN
6	FIN	COM	STA	ENR	COM	DIS	ENR	MAT	TEC	ENR	REA	FIN	MAT
7	REA	MAT	ENR	DIS	HC	ENR	MAT	FIN	MAT	MAT	DIS	MAT	REA
8	COM	STA	FIN	MAT	MAT	TEC	UTL	ENR	UTL	UTL	COM	TEC	HC
9	MAT	ENR	UTL	STA	UTL	HC	TEC	COM	HC	FIN	ENR	REA	ENR
10	STA	FIN	COM	COM	STA	IND	STA	HC	REA	TEC	MAT	DIS	STA
11	HC	UTL	TEC	FIN	FIN	FIN	COM	STA	STA	STA	UTL	COM	UTL

Source: Bloomberg; ENR – Energy; REA – Real Estate; FIN – Financials; UTL – Utilities; STA - Consumer Staples; IND – Industrials; HC - Health Care; MAT – Materials; COM – Communication Services; DIS – Consumer Discretionary; TEC – Information Technology

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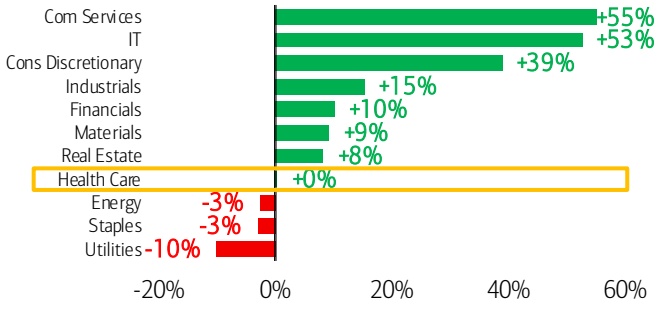
The S&P500 had strong 2023, with only energy, staples, and utilities declining vs 2022. Within the S&P500, we would characterize the performance of Health Care as tepid in 2023, only outperforming 3/11 other GICS sectors, though positive on the year. Taking a closer look at the distinct subsectors within the Health Care GICS, both Biotechnology (+1% y/y in 2023) and Pharmaceuticals (-3% y/y in 2023) performed near the bottom of the healthcare space (see Exhibit 15). Additionally, Biotechnology and Pharmaceuticals underperformed HC Supplies (+21%), HC Distribution (+21%), HC Facilities (+12%), and HC equipment (+7%), while only outperforming relative to Life Science Tools/ Services (-3%) and HC services (-10%). In our view, strength in Biotechnology and Pharmaceuticals should rebound, setting the stage for further growth in 2024.

Exhibit 14: S&P 500 GICS sector performance in 2023 vs 2022
Health Care was flat in 2023, outperforming energy, staples, and utilities



Source: Bloomberg

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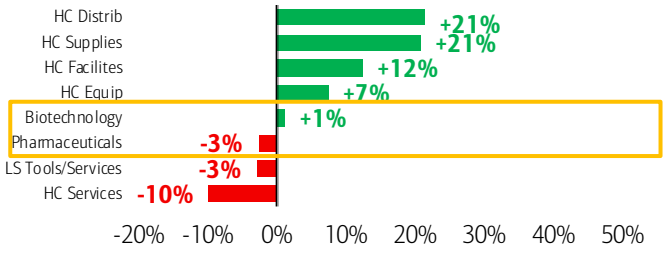
Exhibit 15: HC subsector performance in 2023 relative to 2022
Pharma and Biotechnology were in the bottom three of sub-sector performance, with Health Care Distribution and Health Care supplies performing the best



Source: Bloomberg

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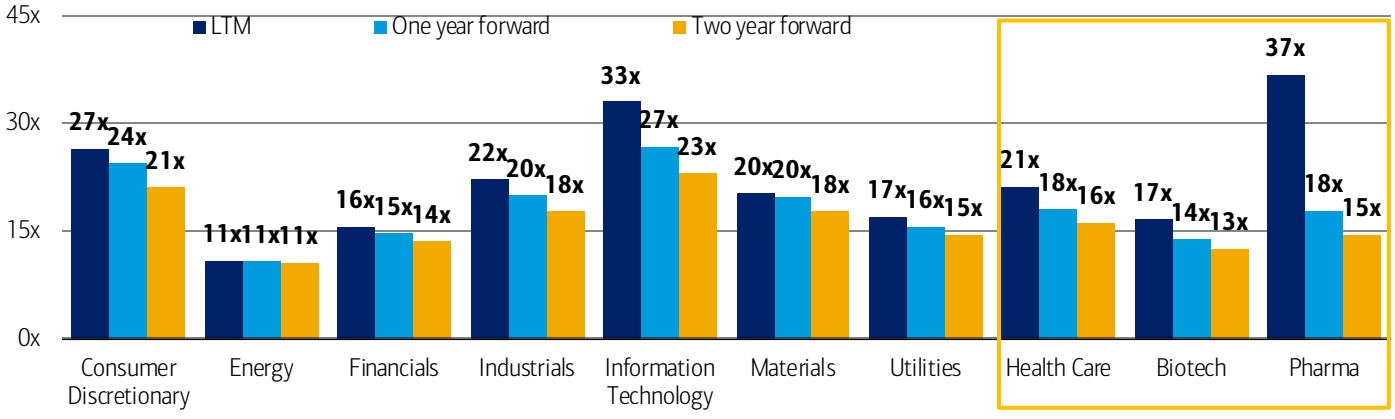
Biotech multiples were pressured in 2023 (LTM), falling short of other GCIS sectors including IT, Industrials, and Consumer Discretionary (see Exhibit 16) given pervasive concerns over maturing portfolios (and associated LOEs/ generic entrants), pipeline uncertainties, and macro headwinds. Pharma's 2023 (LTM) multiples appear inflated by 1-time expenses recognized by Lilly and Merck. Overall Healthcare's 1-year forward P/E (18x) currently ranks in the middle of the S&P500 component subsectors, lower than Consumer Discretionary (25x), Industrials (20x), Materials (20x), and IT (20x), but above Financials (15x), Energy (11x), and Utilities (16x). Moreover, Pharma's (18x) 1-year forward PE is in line with the healthcare average, while Biotech's (14x) is below. In the longer term, 2-year forward PE indicates that both Pharma (15x) and Biotech (13x) are both lower than the GCIS average, suggesting that investors expect healthcare to underperform. Heading into 2024, we expect focus to continue shift away from value and defensive positioning to growth areas more core to Biopharma's long-term development (oncology, gene therapy, etc.) driven by new launches and product cycles. In Biotech more specifically, we suspect continued de-risking of novel technology platforms (mRNA, gene editing, cellular therapies) should re-ignite investor interest and drive multiple expansion.

Exhibit 16: S&P 500 Sector/Industry Outlook: LTM, 1-year, and 2-year forward looking multiples
Biotech forward multiples look cheap versus other sectors while Pharma is in-line



Source: Bloomberg

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Interestingly, these compressed multiples appear to reflect concerns over the sector's near-term growth profile. Over the next year, Health Care is projected to grow revenues +6% (fourth highest among the 11 sectors) while Pharmaceuticals (+5%) and Biotech (+3%) are expected to underperform broader healthcare stocks. Over the next 2 years however, both Pharmaceuticals (+6%) and Biotech (+5%) are expected to see

accelerating revenue growth. Consistent trends are seen in earnings estimates, with Health Care the second highest among 11 sectors at +18% EPS 12-month forecast (see Exhibit 17). Pharma's (48%) 12-month expected EPS growth (off a low base) is projected to outperform healthcare while Biotech's (+7%) 12-month EPS growth is expected to lag broader Health Care, with Pharma's outperformance relative to Biotech coming from both depressed 2023 earnings from 1-time expenses recognized by Lilly and Merck and its defensive nature. Biotech's late 2023 surge looks to continue in 2024 and 2025 which in our view will likely be driven by investors returning to growth names as the macro backdrop improves. Based on these forecasts, we continue to see room for multiple expansion for Biotech in the coming year as Pharma maintains its defensive positioning.

Moreover, we see limited rationale for the declines in the revenue/ earnings growth outlook for Biotech and Pharma over the next 12 months, aside from companies with LOEs of large products. Innovation within the sector continues to advance, with de-risking of more novel technologies and successful product enhancements likely to drive topline growth. Indeed, new launches/readouts (Lilly, Vertex) and product expansions (Gilead, Merck) have the potential to add value to the sector and drive continued earnings growth. Along with a renewed emphasis on execution and strong focus innovation, we continue to believe the sector remains well-positioned for continued robust growth even as macro concerns subside.

Exhibit 17: S&P 500 sector/ industry revenue outlook
Health Care revenue outlook is near the top of GICS sectors for the next 12 months

Sector/ Industry	12 month	24 month
Information Technology	10%	9%
Consumer Discretionary	6%	8%
Communication Services	6%	6%
Health Care	**6%**	**7%**
Real Estate	6%	6%
Industrials	5%	6%
Financials	4%	5%
Consumer Staples	3%	3%
Utilities	3%	3%
Materials	1%	3%
Energy	1%	0%
Pharmaceuticals	**5%**	**6%**
Biotechnology	**3%**	**5%**

Source: Bloomberg

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Exhibit 18: S&P 500 sector/industry earnings outlook
HC Earnings growth is near the top for 2024, but could lag other sectors in 2025

Sector/ Industry	12 month	24 month
Information Technology	23%	16%
Health Care	**18%**	**11%**
Communication Services	17%	11%
Industrials	11%	13%
Utilities	9%	8%
Consumer Discretionary	9%	16%
Financials	6%	8%
Consumer Staples	6%	7%
Materials	2%	12%
Real Estate	2%	11%
Energy	1%	2%
Pharmaceuticals	**48%**	**12%**
Biotechnology	**7%**	**10%**

Source: Bloomberg

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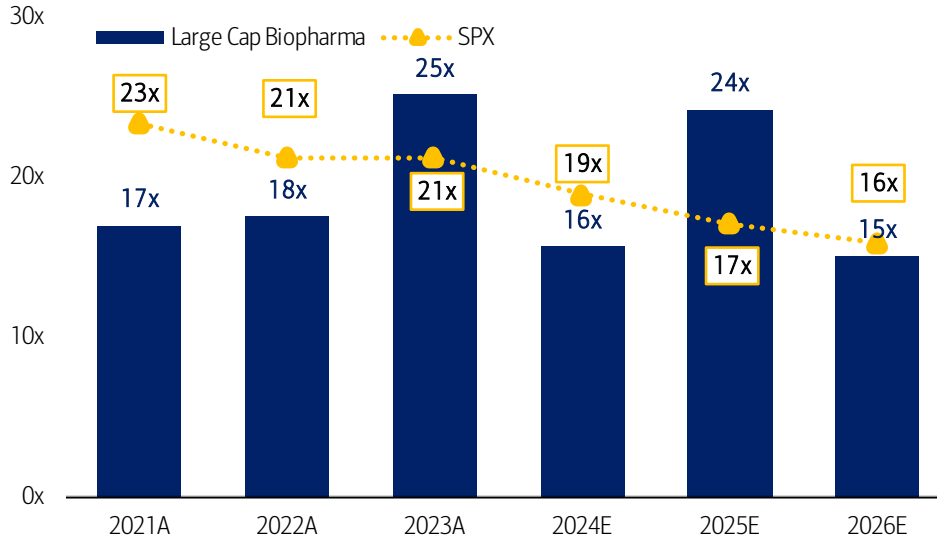
Thus, despite the somewhat negative sentiment over the next 12 months, we remain overall positive on the space. Historically, above-market revenue and earnings growth prospects have been a critical investment driver, which we expect to continue in the near- and mid-term. Given the relatively low expectations (particularly with regards to 12-month revenue/ earnings growth), combined with positive underlying fundamentals, we can see potential for meaningful multiple expansion relative to the S&P500 (see Exhibit 19). Current multiples for US Large Cap Biopharma (our coverage universe) are in line with the broader market, however we see multiple opportunities for value creation in 2023 and beyond especially among companies with strong late-clinical/ early-commercial portfolios, including Vertex's exa-cel as an encore to its cystic fibrosis franchise; Lilly's solid early-stage portfolio and recent high-profile launch in obesity; and Merck's continued expansion of both Keytruda and Gardasil. Interestingly, when looking at Large Cap Biotech (e.g., Biogen, Gilead, Vertex) separately from Pharma (e.g., Pfizer, Bristol), we note greater outperformance in 2023, which we expect to continue in 2024 as investors can play both offense and defense with new product cycles/launches.

Exhibit 19: US Biopharma outlook; 2021A-2026E multiples
Large-cap Biopharma multiples finished 2023 above the broader market, but could fall below in 2024



Source: Bloomberg

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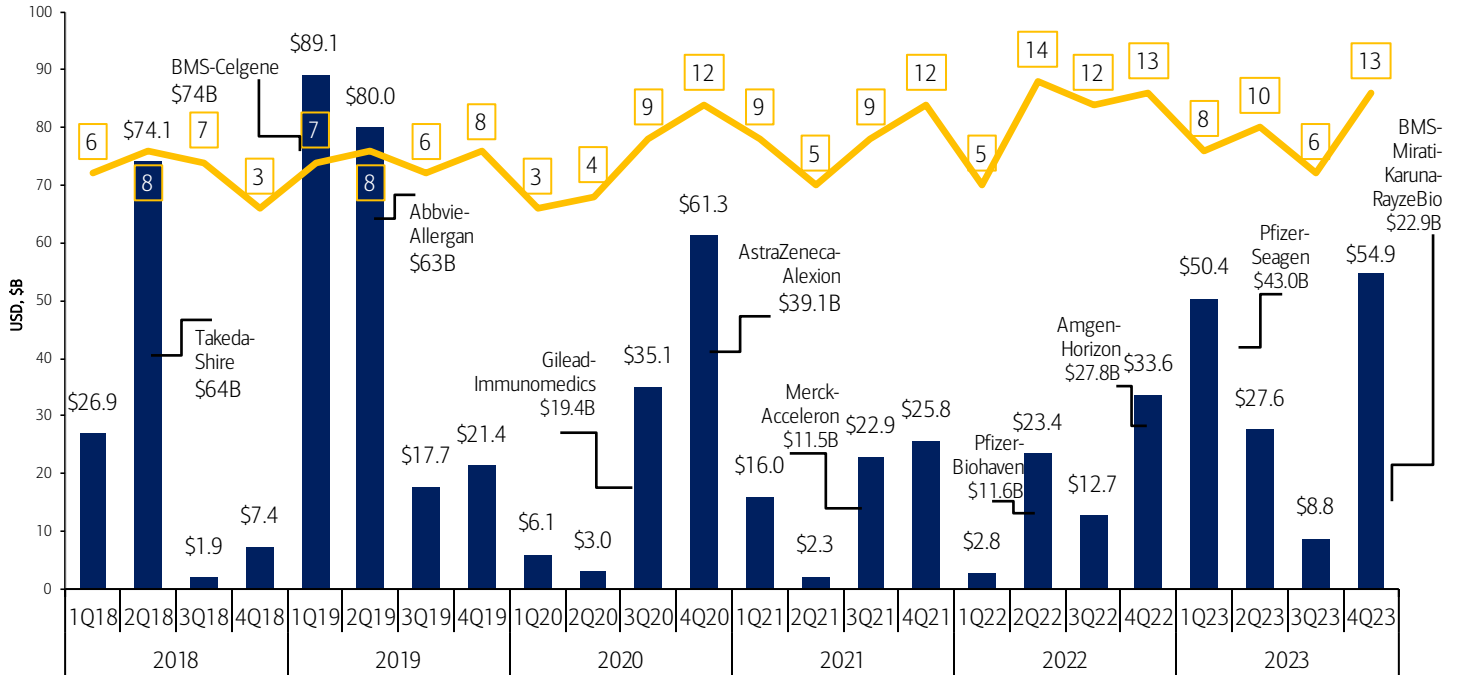
In our view, generalist interest in Biopharma should continue in 2024, driven by continued growth in high-profile indications (obesity and cancer). Indeed, the sector has historically outperformed during economic slowdowns, which will likely further drive investor interest in the space as other sectors (i.e., Tech) no longer provide attractive returns. With the potential tailwind of lower rates, we argue Biopharma provides a defensive place for investors while still offering the potential for significant growth. And as the macro backdrop improves, we argue individual names (Lilly, Merck, Vertex) will continue to outperform the broader sector.

Robust M&A activity in 2023, though some FTC risk remains an overhang into 2024

2023 was a solid year for M&A with total deal value back up to $141.8B, above the $73B in 2022, near the highs seen in 2018-2020 (2018: $110B; 2019: $208B; 2020: $105B). Indeed, the largest deals in 2023 included Pfizer's $43.0B acquisition of Seagen (Pfizer-Seagen deal closing note), AbbVie's combined propsed $18.8B acquisitions of ImmunoGen and Cerevel (see our AbbVie M&A note), and Bristol's proposed combined $22.9B acquisitions of Mirati (Bristol-Mirati note), Karuna (Bristol-Karuna note) and RayzeBio (Bristol-RayzeBio note). That said, we think appetite for M&A/ licensing should remain unabated despite the number of active acquirers and takeout targets has shrunk given LOEs largely remain for majority of large cap Biopharma and majority remain under-levered for meaningful deals. Furthermore, while the Amgen-Horizon and Pfizer-Seagen deals closing in 2023 relieved some regulatory concerns, overall sentiment is that the FTC remains hawkish. The FTC successfully challenged Sanofi's deal with Maze Therapeutics to acquire a Pompe Disease drug and settled on Pfizer-Seagen only after Pfizer agreed to donate its royalties from sales of the cancer drug, Bavencio, to the AACR.

Exhibit 20: Historical M&A activity in Biopharma; deal number, total value, and key transactions, by quarter
2023 was a solid year for M&A with total deal value back up to $141.8B, near the highs seen in 2018-2020 (2018: $110B; 2019: $208B; 2020: $105B).



Source: BioPharma Dive, Company reports; yellow line - volume of deals; blue bars - total deal value

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2023 marked by fewer, but larger deals and premiums

By far, Pfizer's acquisition of Seagen for $43.0B was the largest single deal in 2023, many times larger than the second (Bristol-Karuna, $14.0B) and third (Merck-Prometheus, $10.8B). That said, in all, there were more >$1B deals (20) than smaller deals <$1B (17), especially compared to 2022 where there were 32 deals <$1B and only 11 deals >$1B.

Exhibit 21: Biotech acquisitions, by year and total value paid upfront
2023 was a solid year for M&A with total deal value back up to $124B

Deal Value	2018	2019	2020	2021	2022	2023
Up to $500M	11	10	9	15	26	11

Exhibit 21: Biotech acquisitions, by year and total value paid upfront
2023 was a solid year for M&A with total deal value back up to $124B

Deal Value	2018	2019	2020	2021	2022	2023
$500M to $999M	5	4	7	4	6	6
$1,000M to $4,999M	3	9	8	12	8	12
$5,000M to $9,999M	3	2	1	2	1	4
$10,000M or more	2	4	3	2	2	4

Source: BioPharma Dive; BofA Global Research; values represent deal count.

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Overall, premiums for public companies were comparable to 2022. Looking ahead, we expect pressure to acquire assets with near-term commercial prospects (late-stage assets) and interest rate easing as factors that may skew premiums lower as the focus shifts to more development stage acquisitions.

Exhibit 22: Biotech acquisitions, by year and percent premium paid
Premium over last closing price were spread pretty evenly; values represent deal count.

Deal premium	2018	2019	2020	2021	2022	2023
0% to 24%	1	1	2	4	5	5
25% to 49%	2	2	3	2	6	5
50% to 74%	6	6	4	3	4	4
75% to 99%	2	1	3	4	4	7
100% or more	2	6	5	3	7	6

Source: BioPharma Dive; BofA Global Research; values represent deal count and only includes publicly traded companies.

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On therapeutic themes, we'd note that within cancer, ADC was by far the most popular modality, with Pfizer, AbbVie, Merck, and Bristol all acquiring multiple ADC assets in 2023. Looking ahead to 2024, we see a growing interest in metabolic diseases / GLP-1 assets, given the large market opportunity, and orphan diseases, given exclusion from IRA drug price negotiations. In particular, we think NASH assets may be in vogue again, following a productive year, which included advancement of two assets to regulatory review (though one of these two assets was not approved) and two promising assets to pivotal studies.

Exhibit 23: Biotech acquisitions, by year and therapeutic category
Deals represented a broad range of therapeutic categories in 2023

Therapeutic Category	2018	2019	2020	2021	2022	2023
Cancer	10	7	6	9	11	7
CNS	1	6	2	4	3	7
Immune	2	3	5	4	5	6
Other	5	6	10	13	17	12
Rare	6	7	5	5	7	5

Source: BioPharma Dive; BofA Global Research; values represent deal count.

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2024 deal capacity down compared to 2023

Going into 2024, we think many would-be buyers have pivoted into focusing on execution with late-stage assets already in-hand from deals in 2023. That said, we don't think Biopharma is over-levered as of yet. Of the remaining large-cap pharma companies with strong balance sheets to deploy, we see J&J, Merck, Novo Nordisk, Novartis, and Biogen as the most likely to be active in 2024 based on strategic need and relatively flexible leverage status.

Exhibit 24: Large Biopharma cash position as of 3Q23 (adjusted for 4Q23 deals)
Of the remaining large-cap pharma companies with strong balance sheets to deploy, we see J&J, Merck, Novo Nordisk, and Biogen as the most likely to be active in 2024 based on strategic need and relatively flexible leverage status

$ M		Cash, Equivalents, & LT Investments	Total Debt	Net Debt	EBITDA (2024e)	Net Leverage Ratio
Biotech						
Amgen	AMGN US Equity	34,741	60,468	25,727	17,449	1.47
Biogen	BIIB US Equity	2,288	7,715	5,427	9,731	0.56
Gilead	GILD US Equity	8,020	24,982	16,962	12,745	1.33
Moderna	MRNA US Equity	7,573	1,455	-6,118	-2,930	N/A
Regeneron	REGN US Equity	15,692	2,703	-12,990	5,409	N/A
Vertex	VRTX US Equity	11,928	745	-11,184	5,114	N/A
Major Pharma						
AbbVie*	ABBV US Equity	13,290	78,946	65,656	26,653	2.46
Bristol*	BMY US Equity	8,010	59,267	51,257	20,366	2.52
Merck	MRK US Equity	8,773	34,859	26,086	29,492	0.88
Pfizer**	PFE US Equity	32,181	63,596	31,415	19,726	1.59
J&J	JNJ US Equity	23,511	29,921	6,410	32,552	0.20
LLY*	LLY US Equity	2,494	21,568	19,074	14,765	1.29
EU Pharma						
AstraZeneca	AZN US Equity	5,115	28,576	23,461	18,115	1.30
GlaxoSmithKline^	GSK US Equity	8,157	25,432	17,275	13,067	1.32
Novartis	NVS US Equity	12,695	25,189	12,494	19,129	0.65
Novo Nordisk^	NVO US Equity	6,751	3,764	-2,987	20,063	N/A
Roche*^	RHHBY US Equity	8,393	38,174	29,781	27,802	1.07
Sanofi^	SNY US Equity	9,731	22,957	13,226	16,044	0.82
Total:		219,343	530,317	310,974	305,290	1.02

Source: Bloomberg, Company Reports, BofA Global Research
*includes deals announced in 4Q23
**includes Pfizer-Seagen deal that has closed
***converted to $USD

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Late stage/ commercial assets remain attractive, though with a focus on smaller market caps

Of the potential M&A targets we listed for 2023, only 4 out of 35 were taken out (Seagen, Myovant, Mirati, Karuna). We had initially screened for companies valued between $2.5B and $40B and expected to generate >$1B revenue in 2026. Looking ahead to 2024, we think that these criteria remain relevant, though preference for smaller companies is likely given increased FTC scrutiny, high premiums demanded for such companies and less cash to deploy. As such, we think companies valued between $1-5B may be more attractive than companies >$5B in 2024.

Specifically, we see Biogen doubling down on its investments in neurodegenerative diseases and J&J looking to further diversify its portfolio with CNS and rare disease. That said, while not a strategic focus, Regeneron and Vertex may be more inclined to engage in M&A as well due to the company's strong balance sheets. Notably, Regeneron has expressed interest in growing the company's gene therapy franchise and deepening its CNS portfolio.

Exhibit 25: Mid-size biotech companies with late-stage/ commercial assets
List of Biotech companies that have a market cap between $1B and $5B with ≥$1B expected revenue in 2026e

Name	Symbol	MarketCap ($B)	Rev (2026e, $B)	Country
Halozyme Therapeutics	HALO	4.9	1.5	United States
ACADIA Pharmaceuticals	ACAD	4.8	1.6	United States
Alkermes	ALKS	4.6	1.7	Ireland
Madrigal Pharmaceuticals	MDGL	4.4	2.1	United States
Evotec	EVO	4.1	1.3	Germany
Insmed Incorporated	INSM	4.1	1.3	United States
Lantheus Holdings	LNTH	4.0	2.1	United States
Ultragenyx	RARE	3.7	1.3	United States
Axsome Therapeutics	AXSM	3.4	1.6	United States
Arrowhead Pharmaceuticals	ARWR	3.1	0.8	United States
HUTCHMED	HCM	2.9	1.1	Hong Kong

Exhibit 25: Mid-size biotech companies with late-stage/ commercial assets
List of Biotech companies that have a market cap between $1B and $5B with ≥$1B expected revenue in 2026e

Name	Symbol	MarketCap ($B)	Rev (2026e, $B)	Country
ImmunityBio	IBRX	2.8	1.4	United States
Zai Lab	ZLAB	2.6	1.3	China
PTC Therapeutics	PTCT	2.1	1.0	United States
Harmony Biosciences	HRMY	1.9	1.3	United States
Amylyx Pharmaceuticals	AMLX	1.0	0.9	United States

Source: BofA Global Research, Bloomberg, Company Reports

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Among would-be buyers in 2024e, we see J&J and Novo as most likely to engage in mega deals valued >$20B based on the companies' deal capacity.

Exhibit 26: Larger biotech companies with late-stage/ commercial assets
List of Biotech companies that have a market cap ≥$9B with ≥$1B expected revenue in 2026e

Name	Symbol	MarketCap ($B)	Rev (2026e, $B)	Country
Alnylam	ALNY	24.2	4.0	United States
Genmab	GMAB	20.9	4.0	Denmark
BeiGene	BGNE	19.1	6.2	China
BioMarin	BMRN	18.1	4.1	United States
Incyte	INCY	14.1	5.5	United States
Viatris	VTRS	12.8	15.5	United States
Neurocrine Biosciences	NBIX	12.6	3.2	United States
Teva Pharmaceutical Industries	TEVA	11.7	16.4	Israel
United Therapeutics	UTHR	10.3	3.2	United States
Sarepta Therapeutics	SRPT	8.8	3.6	United States

Source: BofA Global Research, Bloomberg, Company Reports

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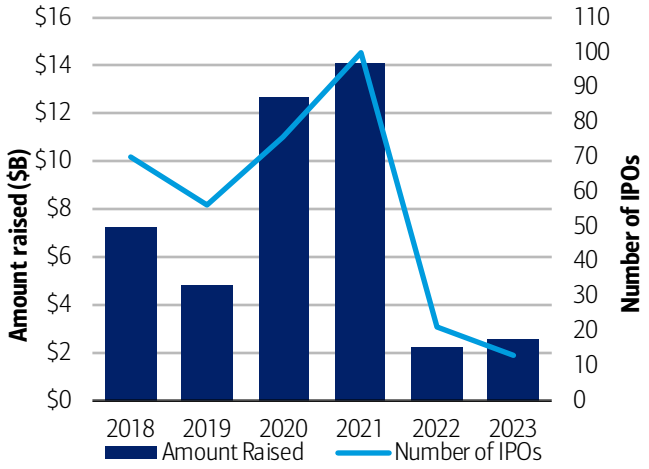
2023: A Lackluster Year for Biotech IPOs

2023 total IPOs were down y/y for the second year in a row with only 13 biotech companies going public (vs. 21 in 2022 and 100 in 2021). However, total proceeds of 2.6B were up slightly in 2023 (vs. $2.2B in 2021 and $12.7B in 2020). We suspect the unfavorable macro environment (e.g., inflation concerns and rising interest rates) and underperforming sector (2023 XBI: +10%, 2023 SPX: +25%) were the main reasons. Additionally, with many early-stage (e.g., pre-clinical) biotech companies made to the public in 2020/2021, it takes time for private biotech companies to develop the next wave of innovative assets and restart the cycle. That said, among the 13 companies that came to market in 2023 we saw a trend of the market favoring companies in commercial stage/ late-stage clinical development (54% late stage/commercial; pre-clinical: 15%). Furthermore, most of the IPOs this year continue to be more heavily weighted in certain disease areas of focus, such as cancer (23%), inflammation and immunology (23%), Neurology (16%), cardiology (15%) and metabolic diseases (15%). Looking to 2024, we expect a recovery of the IPO market, and the trend of favoring more mature companies in certain disease areas will likely continue in 2024.

Exhibit 27: Biotech IPOs and proceeds from 2018-2023 (quarterly)
2023 IPO proceeds were the second lowest in 5 years



Source: BofA research; BioPharma Dive

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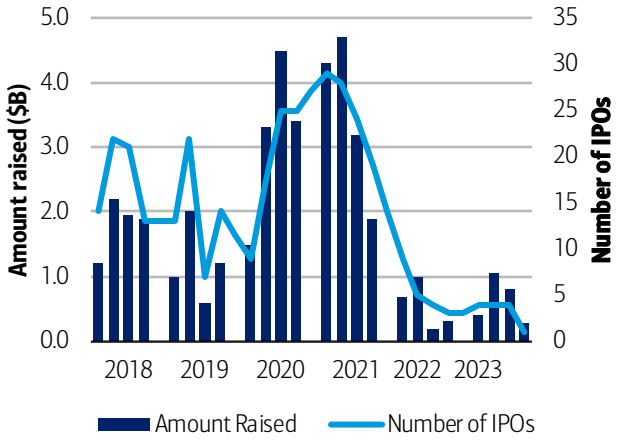
Exhibit 28: Biotech IPOs and proceeds from 2018-2023 (annually)
2023 was a lackluster year for biotech IPOs (by #)



Source: Bofa research; BioPharma Dive

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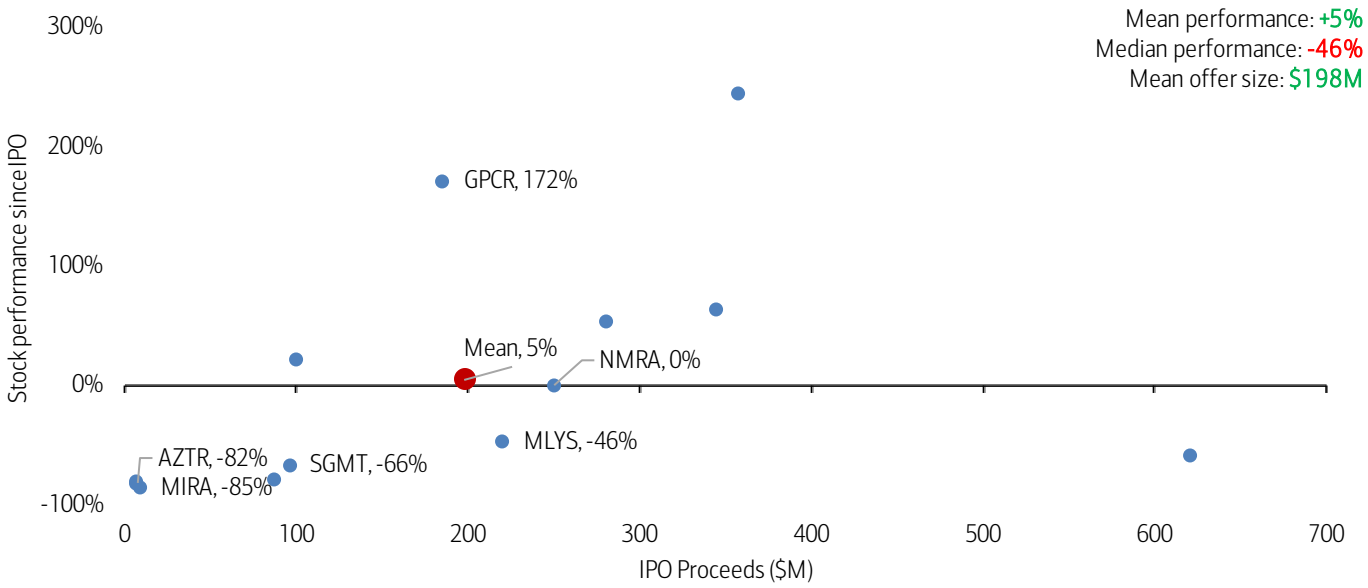
2023 IPO performance defined by standouts

Overall, the IPO class of 2023 outperformed the biotech sector (2023 XBI: -1%), with a mean return of +4% and a median return of -46%, compared to the IPO offer price. That said, the solid mean return was largely driven by a few companies including Structure Therapeutics, Apogee Therapeutics, Cargo Therapeutics, and Lexeo Therapeutics (*Exhibit 29*).) We think their outperformance was driven by their multiple shots on goal approach to their pipeline, all four of these winners are clinical-stage biotech companies with multiple pipeline candidates. That said, no clear trend in therapeutic area and modality was observed. Overall, the results aren't a surprise to us as under challenging macro environment, biotech companies with solid data and clinical progress are likely to outperform peers. In contrast, shares of pre-clinical companies with no near-term data catalyst suffered the most in 2023. Looking to 2024, we think the increase on certainty and positive sentiment on macro conditions (e.g., Fed's interest rate) in 2024 will likely contribute to a more balanced IPO class next year.

Exhibit 29: Stock performance for Biotech IPOs launched in 2023
2023 was a tough year for biotech IPO performance



Source: BofA research; Bloomberg

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Exhibit 30: Four 2023 Biotech IPOs with solid stock performance
Outperformance was driven by clinical progress and investor optimism

Ticker	Company Name	Therapeutic Area (details)	Modality	No. of Pipeline Candidates	Stage (lead candidate)	Current Market Cap (M)	Offer To Date
GPCR US	Structure Therapeutics Inc	GLP-1	Metabolic	Multiple	Phase 2	1891	172%
APGE US	Apogee Therapeutics Inc	Atopic Dermatitis	Immunology	Multiple	Phase 1	1416	64%
CRGX US	Cargo Therapeutics Inc	Cancer	Cancer	Multiple	Preclinical	954	54%
LXEO US	Lexeo Therapeutics Inc	FA cardiomyopathy	Cardiology	Multiple	Phase 1	358	22%

Source: BofA research; Company filings

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Profile of companies that made to the public in 2023

We took a deep dive to understand the 2023 IPO class in terms of therapeutic area (Exhibit 31), development stage (Exhibit 32), modality (Exhibit 33), and the number of pipeline candidates (Exhibit 34).

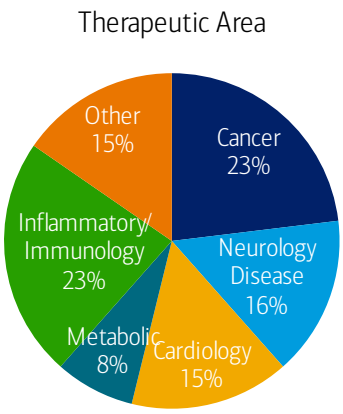
Therapeutic area: Not surprisingly, cancer (23%) is still the key therapeutic area for investors. That said, beyond cancer, other key focus areas for investors are correlated to hot topics in the biopharma sector. For example, high profile data readouts and approvals of GLP-1s for obesity (Novo's Wegovy, Lilly's Zepbound) were arguably the hottest topic of 2023, which correlates to the high number of IPO companies that develop drug candidate for obesity (8% of 2023 biotech IPOs)

Development stage: Among the 2023 IPO companies, only 15% are pre-clinical stage companies, while >50% of them are late/ commercial-stage companies. In contrast, many pre-clinical stage biotech companies went public in 2020/ 2021. That said, we think current market conditions will continue to favor more mature biotech companies in 2024.

Modality: In our analysis of the 2023 IPO class, the percentage of companies that develop small molecule, biologic, and cell/gene therapy are 38%, 39%, and 23%, respectively. The comparatively low number of small molecule IPO candidates could be due to the Inflation Reduction Act (IRA), as it favors biologics vs. small molecule drugs by imposing price controls on biologics at 13 years after launch vs. small molecules at 9 years.

No. of pipeline candidates: Among biotech companies that went public in 2023, most of them (81%) have multiple pipeline candidates. That said, although most companies have multiple assets in the pipeline, the lead assets are commonly well ahead in development stage and account for most of the valuation.

Exhibit 31: 2023 biotech IPOs by therapeutic area
No clear preference of therapeutic focus



Source: BofA research

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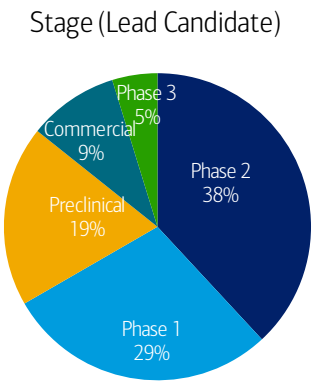
Exhibit 32: 2022 biotech IPOs by stage
Most biotech IPOs are early stage companies



Source: BofA research

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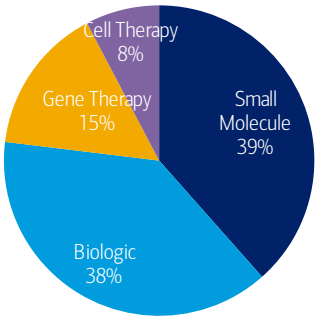
Exhibit 33: 2023 biotech IPOs by modality
No clear preference of small molecule vs. biologic



Source: BofA research

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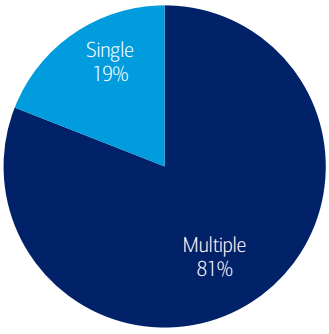
Exhibit 34: 2023 biotech IPOs by No. of pipeline candidates
Most of biotech IPOs have multiple pipeline candidates



Source: BofA research

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FDA year-in-review and 2024 initiatives

Compared to the year prior, FDA approvals in 2023 have returned to prior levels with 53 approvals compared to only 33 approvals in 2022 (53 in 2020 and 50 in 2021). We think the increased productivity of FDA in 2023 bodes well for 2024 and may also reflect an end to COVID-era impact on clinical trial enrollment (for trials initiated in 2019).

Exhibit 35: 2023 New Drug Approvals
FDA approvals in 2023 have returned to prior levels with 53 approvals compared to only 33 approvals in 2022.

Novel Drug Approvals for 2023 | FDA			
Drug Name	**Active Ingredient**	**Approval Date**	**FDA-approved use on approval date***
Fabhalta	iptacopan	12/5/2023	To treat paroxysmal nocturnal hemoglobinuria
Ogsiveo	nirogacestat	11/27/2023	To treat adults with progressing desmoid tumors who require systemic treatment
Truqap	capivasertib	11/16/2023	To treat breast cancer that meets certain disease criteria
Ryzneuta	efbemalenograstim alfa-vuxw	11/16/2023	To treat neutropenia
Augtyro	repotrectinib	11/15/2023	To treat ROS1-positive non-small cell lung cancer
Defencath	taurolidine, heparin	11/15/2023	To reduce the incidence of catheter-related bloodstream infections in adults with kidney failure receiving chronic hemodialysis through a central venous catheter
Fruzaqla	fruquintinib	11/8/2023	To treat refractory, metastatic colorectal cancer
Loqtorzi	toripalimab-tpzi	10/27/2023	To treat recurrent or metastatic nasopharyngeal carcinoma when used together with or following other therapies
Omvoh	mirikizumab-mrkz	10/26/2023	To treat ulcerative colitis
Agamree	vamorolone	10/26/2023	To treat Duchenne muscular dystrophy
Bimzelx	bimekizumab	10/17/2023	To treat moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Zilbrysq	zilucoplan	10/17/2023	To treat generalized myasthenia gravis in adults who are anti-acetylcholine receptor (AChR) antibody positive
Velsipity	etrasimod	10/12/2023	To treat moderately to severely active ulcerative colitis in adults
Rivfloza	nedosiran	9/29/2023	To lower urinary oxalate levels in patients 9 years and older with primary hyperoxaluria type 1 and relatively preserved kidney function
Pombiliti	cipaglucosidase alfa-atga	9/28/2023	To treat late-onset Pompe disease
Exxua	gepirone	9/22/2023	To treat major depressive disorder
Ojjaara	momelotinib	9/15/2023	To treat intermediate or high-risk myelofibrosis in adults with anemia
Aphexda	motixafortide	9/8/2023	To use with filgrastim (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma
Veopoz	pozelimab-bbfg	8/18/2023	To treat patients 1 year old and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease
Sohonos	palovarotene	8/16/2023	To reduce the volume of new heterotopic ossification in adults and pediatric patients (aged 8 years and older for females and 10 years and older for males) with fibrodysplasia ossificans progressiva
Elrexfio	elranatamab-bcmm	8/14/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy
Talvey	talquetamab-tgvs	8/9/2023	To treat adults with relapsed or refractory multiple myeloma who have received at least four prior therapies
Izervay	avacincaptad pegol	8/4/2023	To treat geographic atrophy secondary to age-related macular degeneration
Zurzuvae	zuranolone	8/4/2023	To treat postpartum depression Press Release
Xdemvy	lotilaner	7/25/2023	To treat Demodex blepharitis
Vanflyta	quizartinib	7/20/2023	To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria
Beyfortus	nirsevimab-alip	7/17/2023	To prevent respiratory syncytial virus (RSV) lower respiratory tract diseasePress Release
Ngenla	somatrogon-ghla	6/27/2023	To treat growth failure due to inadequate secretion of endogenous growth hormone
Rystiggo	rozanolixizumab-noli	6/26/2023	To treat generalized myasthenia gravis in adults who are anti-acetylcholine receptor- or anti-muscle-specific tyrosine kinase antibody-positive
Litfulo	ritlecitinib	6/23/2023	To treat severely patchy hair loss
Columvi	glofitamab-gxbm	6/15/2023	To treat diffuse large B-cell lymphoma, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma after two or more lines of systemic therapy
Inpefa	sotagliflozin	5/26/2023	To treat heart failure
Posluma	flotufolastat F 18	5/25/2023	To use with positron emission tomography imaging in certain patients with prostate cancer
Paxlovid	nirmatrelvir, ritonavir	5/25/2023	To treat mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19Press Release
Xacduro	sulbactam, durlobactam	5/23/2023	To treat hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complexPress Release
Epkinly	epcoritamab-bysp	5/19/2023	To treat relapsed or refractory diffuse large B-cell lymphoma (not otherwise specified) and high-grade B-cell lymphoma after two or more lines of systemic therapy
Miebo	perfluorhexyloctane	5/18/2023	To treat signs and symptoms of dry eye disease
Veozah	fezolinetant	5/12/2023	To treat moderate to severe hot flashes caused by menopausePress Release
Elfabrio	pegunigalsidase alfa-iwxj	5/9/2023	To treat confirmed Fabry disease
Qalsody	tofersen	4/25/2023	To treat amyotrophic lateral sclerosis in adults who have a SOD1 gene mutation
Joenja	leniolisib	3/24/2023	To treat activated phosphoinositide 3-kinase delta syndrome
Rezzayo	rezafungin	3/22/2023	To treat candidemia and invasive candidiasis
Zynyz	retifanlimab-dlwr	3/22/2023	To treat metastatic or recurrent locally advanced Merkel cell carcinoma
Daybue	trofinetide	3/10/2023	To treat Rett syndrome
Zavzpret	zavegepant	3/9/2023	To treat migraine
Skyclarys	omaveloxolone	2/28/2023	To treat Friedrich's ataxia
Filspari	sparsentan	2/17/2023	To reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression
Lamzede	velmanase alfa-tycv	2/16/2023	To treat non-central nervous system manifestations of alpha-mannosidosis

Exhibit 35: 2023 New Drug Approvals
FDA approvals in 2023 have returned to prior levels with 53 approvals compared to only 33 approvals in 2022.

Novel Drug Approvals for 2023 | FDA			
Jesduvroq	daprodustat	2/1/2023	To treat anemia caused by chronic kidney disease for adults on dialysis for at least four monthsPress Release
Orserdu	elacestrant	1/27/2023	To treat estrogen receptor-positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy
Jaypirca	pirtobrutinib	1/27/2023	To treat relapsed or refractory mantle cell lymphoma in adults who have had at least two lines of systemic therapy, including a BTK inhibitor
Brenzavvy	bexagliflozin	1/20/2023	To improve glycemic control in adults with type 2 diabetes mellitus as an adjunct to diet and exercise
Leqembi	lecanemab-irmb	1/6/2023	To treat Alzheimer's disease

Source: FDA, BofA Global Research

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Separately, the FDA also approved a number of biologics, most notably vaccines for RSV and gene therapy treatments for blood disorders.

Exhibit 36: 2023 New Biologics Approvals
We'd call out approval of RSV vaccines and gene therapies as significant for the industry

Novel Biologics Approvals for 2023 | FDA			
Drug Name	**Active Component / Intended Use**	**Approval Date**	**Indication for Use**
Penbraya	Meningococcal Groups A, B, C, W, and Y Vaccine	10/20/2023	Indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroups A, B, C, W, and Y. Meningococcal Groups A, B, C, W, and Y Vaccine is approved for use in individuals 10 through 25 years of age.
Abrysvo	Respiratory Syncytial Virus Vaccine	8/21/2023	Indicated for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age.
Balfaxar	prothrombin complex concentrate, human-lans	7/21/2023	Indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.
Cyfendus	Anthrax Vaccine Adsorbed, Adjuvanted	7/20/2023	Indicated for post-exposure prophylaxis of disease following suspected or confirmed exposure to Bacillus anthracis in persons 18 through 65 years of age when administered in conjunction with recommended antibacterial drugs.
Roctavian	valoctocogene roxaparvovec-rvox	6/29/2023	Valoctocogene roxaparvovec-rvox is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.
Lantidra	donislecel-jujn	6/28/2023	Indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.
Elevidys	delandistrogene moxeparvovec-rokl	6/22/2023	Indicated for treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.
Abrysvo	Respiratory Syncytial Virus Vaccine	5/31/2023	Indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older.
Vyjuvex	beremagene geperpavec-svdt	5/19/2023	Indicated for treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.
Arexvy	Respiratory Syncytial Virus Vaccine, Adjuvanted	5/3/2023	Indicated for active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older.
Vowst	fecal microbiota spores, live-brpk	4/26/2023	To prevent the recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI).
Omisirge	omidubicel-onlv	4/17/2023	Indicated for use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.
Altuviio	antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl	2/22/2023	Indicated for use in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; and (3) Perioperative management of bleeding.

Source: FDA, BofA Global Research

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Takeaways from FY 2024 Legislative Proposals

While FDA's $7.2B budget includes several legislative proposals, which provide some insight into the organization's key initiatives, we highlight three updates which we think have potential read-through to the biopharma and biotech industry.

> "**Postmarket Safety Collaborative:** +$10.1 million for a total of $36.8 million to enhance safety surveillance and oversight programs to develop more efficient and effective detection, evaluation, prevention, and mitigation of adverse events. Protecting the health of humans and animals requires FDA to continuously enhance its safety surveillance and oversight programs, consistent with advances in the science of drug and device safety. New scientific approaches and improved tools are available and needed for the efficient and effective detection, evaluation, prevention, and mitigation of adverse events."

Calls for increased budget in postmarket safety surveillance coincide with the FDA's announcement in 2023 about ongoing investigation into the post-secondary malignancy risk of CAR-T cell therapies. While most KOL's we've spoken to maintain that the clinical benefit outweighs risk in heme/onc, we could see some negative read-through on the development of CAR-T for certain I&I indications (see our ASH 2023 note of CAR-T toxicities). An investigation into the 19 CAR-T secondary malignancy reports (12 were cases of T-cell lymphoma reported by patients using the FDA Adverse Events Reporting System or FAERS, remaining cases are from clinical trials) is ongoing, and we do not expect for there to be any major changes in clinical practice even if are there updates to the safety label of CAR-T's.

> "**ACT for ALS:** +$2.5 million for a total of $7.5 million to implement the ACT for ALS, including the ability to issue new grants and contracts, hire dedicated expert staff, and allow FDA to facilitate access to investigational therapies and medical devices for neurodegenerative diseases such as amyotrophic lateral sclerosis (i.e., ALS, also known as Lou Gehrig's disease, a progressive and fatal disease)."

Despite some initial regulatory setbacks and negative feedback from EU regulators in 2023, Amylyx's Relyvrio, which was only the third drug approved to treat ALS, has had robust uptake commercially. Combined with the FDA's commitment to advance ALS drugs, we overall remain bullish on the outcome of the larger 600-person trial set to read out in 2024. Furthermore, while Leqembi's passage (see our note on Leqembi approval) has paved the path for approval, we remain interested in Lilly's donanemab full approval and the development of other neurodegenerative disease treatments, including AbbVie's late-stage Parkinson Disease treatments.

> "***Expansion of FDA Tools to Provide Oversight of FDA-Regulated Products:*** *This proposal will promote regulatory compliance and help to protect the public health, particularly during a public health emergency like the COVID-19 pandemic where in-person inspections and investigations were limited, by allowing FDA to conduct certain oversight activities prior to arriving for or instead of an inspection, thus improving the efficiency of FDA resources and reducing FDA's on-site inspectional time, and by allowing the FDA to assess conditions at a facility without going onsite when an in-person visit is not feasible or deemed necessary by FDA."*

With delay to regulatory review of Iovance's TIL as one of the more recent examples, we think the FDA's interest in digital tools to support virtual inspections should help decrease delays to regulatory review as a result of CMC-related (chemistry, manufacturing, and controls) limitations. Especially as more cell and gene therapies are under development to treat an increasingly broad spectrum of diseases, we see an increased need for the FDA to invest in its CMC review capacity given the complexity of cell and gene therapy manufacturing.

Looking Forward to 2024

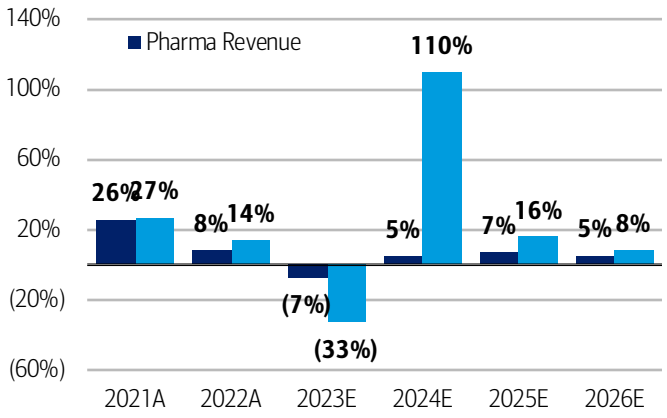
2023 was a roller coaster ride – quality growth names continued to win (Lilly, Vertex) while COVID/ execution story fell flat (Pfizer, Moderna, Bristol). Importantly, it appears that the M&A and deal making activities are finally back in full force, including a string of potential acquisitions that were all announced during the last month of the year (Immunogen, Cerevel, Karuna, RayzeBio). Overall, Large caps were mostly defensive while SMids were depressed for the better part of that year, bottoming to 5-year low in October. That said, the reversal of fortune occurred with the help of more dovish view from the Fed in conjunction with the pickup of deal activities. While both Large and SMiDs indices underperformed the broader market and tech YTD (DRG: +5%, NBI +4%, XBI +8%, S&P +24%, NDX +56%), we're optimistic heading into 2024 given pharma/biotech's attractive valuations and robust M&A/licensing deals will remain robust next year.

We expect M&A/licensing deals to remain elevated driven given the clear line of sight on looming LOE and the uncertainty around IRA impact. Despite several sizable M&A and partnership deals in 2023, there's still a meaningful gap between the loss of sales from LOE versus expected sales obtained from recent acquisitions. Importantly, majority of the large BioPharma names remain "under-levered" (<2.5 net debt/'24 EBITDA), suggesting that there's still plenty of M&A firepower left for deals to be made. Indeed, only AbbVie and Bristol are at net leverage capacity (~2.5x) according to our analysis. That said, we do not envision Pfizer to do any sizable deal in the near-term as it focuses on integrating Seagen business and transforming the company into an oncology-focus biopharma. On the other hand, we look forward to seeing more activities from Amgen, Biogen, Merck and J&J in 2024 given their needs to grow through LOE in 2025+. Importantly, there are several key data readouts from SMids in 2024 which could drive meaningful upside on their outlook and their potential as M&A targets, including Amylyx and Neumora. To that end, we expect the upward share/sentiment momentum on SMids to continue into next year.

2024 will continue to be the year of "haves" vs "have nots" for large BioPharma
With declining COVID revenue largely in the rearview mirror, Major Pharma is expected to see revenue growth return (Cons +5% y/y), driven largely by Lilly's Mounjaro/ Zepbound (+114% y/y), followed by Merck's Keytruda/ Gardasil (+12% y/y). For Pfizer, growth from the incremental Seagen's revenue and new launches will be largely offset by continued COVID decline (-23% y/y). Bristol and J&J are expected to see modest growth this year supported by new products launches but Revlimid and Stelara LOEs will continue to weigh on growth through 2025. On the other hand, 2024 is expected to be the floor for AbbVie given Humira patent cliff/ Imbruvica competition more than offset otherwise strong growth from the rest of the business. Of note, earnings growth for 2024 is unreliable given the number of large M&A in 2023 that severely impacted 2023 earnings.

In large cap Biotech, we expect to see an overall solid growth in revenue (Cons. +6% y/y) and earnings (+6%). That said, Biogen revenue is expected to continue to decline due to declining core business (SMA and MS) due to generic entry/competition and it will take time for Leqembi/ Skyclaris to provide meaningful contribution. Gilead will be back to growth trajectory (+2% y/y) driven by both the HIV and oncology portfolio (Yescarta/Trodelvy). Regeneron will likely have another solid year (+6% y/y) driven by continued Dupixent growth and HD Eylea launch, but long-term outlook remains uncertain due to Eylea competition from Roche's Vabysmo and biosimilars. Vertex will continue to be the winner among Large Biotech in 2024 with continued strength from Trikafta and key late-stage readouts in acute pain. 2024 will be an important year for Amgen given the obesity portfolio focus as we await AMG133 phase 2 data in 2H24. That said, the rest of portfolio appears lackluster with uncertainty on long-term growth outlook; as such we could potentially see more BD activity, especially if AMG133 results miss the mark.

Exhibit 37: Major US Pharma Rev./EPS Expected Annual Growth Rates
Large M&A/licensing deals in 2023 affecting the growth rates



Source: Bloomberg, Companies include Pfizer, AbbVie, Merck, Lilly, Bristol, J&J
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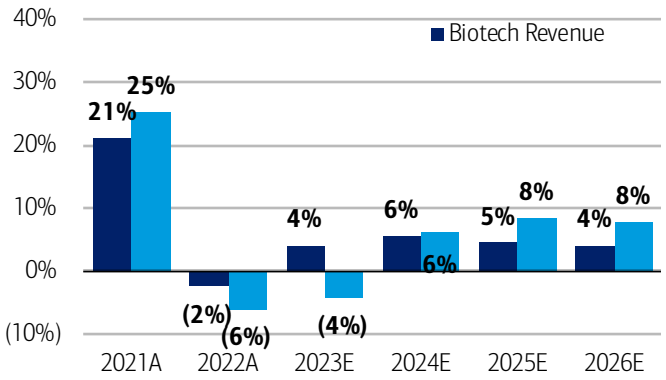
Exhibit 38: Large Cap Biotech Rev./EPS Expected Annual Growth Rates
Large M&A/licensing deals in 2023 affecting the growth rates



Source: Bloomberg: Companies include Amgen, Biogen, Gilead, Regeneron, Vertex
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Policy & Regulatory outlook – Andy Bressler

FY2024 Government Funding

As we begin 2024, Congress still needs to address FY2024 government funding to avoid a potential government shutdown, as we approach the next deadline of January 19, 2024. From a healthcare perspective, the good news is that Medicare and Medicaid payments are not impacted by a government shutdown. However, other agencies, including NIH, FDA, CDC and others would be impacted if Congress is unable to reach agreement by January 19 (or February 2, the next looming deadline). Congress was able to avoid a government shutdown on November 17 with a Continuing Resolution (CR) to fund the government through January 19 (and February 2). The bill also provided funding for Community Health Centers and delayed pending Medicaid Disproportionate Share (DSH) payment cuts to hospitals, but, only until January 19. When Congress returns in early January, it will need to find an agreement on government funding quickly, either through another short-term CR, or potentially look at a year-long Continuing Resolution to fund the government through the remainder of FY2024.

Implementation of IRA Drug Pricing Reforms

CMS continues to move forward with implementation of the Inflation Reduction Act (IRA), and its Medicare drug price negotiation process. In August, CMS announced the selection of the first 10 Medicare Part D drugs for negotiation.

In total, CMS notes that the 10 selected Medicare Part D drugs accounted for more than $50 billion in gross Medicare Part D drug spending from June 2022 through May 2023. These 10 drugs represent roughly 20% of gross Medicare spend. CMS estimates that "over 8 million" Medicare beneficiaries used the 10 selected drugs, with 3.5 million beneficiaries taking Eliquis, and 1.3 million taking Jardiance and 1.3 million taking Xarelto. CMS also notes that out-of-pocket spending for these 10 drugs ranged from $261 per enrollee for NovoLog to a high of $6,497 per enrollee for Imbruvica.

With the selection of the first 10 Medicare Part D drugs for negotiation, drug manufacturers signed agreements to participate in the negotiation program and submit information on the drugs in October. CMS held public listening sessions for each drug in October and November. CMS will send its initial drug pricing proposal to manufacturers, along with justification for its price by February 1, 2024, and companies will then have 30 days to respond. Additional negotiation meetings will then take place in the spring and summer 2024, with the negotiation period ending on August 1, 2024. CMS will then release the final payment amounts for each drug by September 1, 2024.

Exhibit 39: CMS 10 Medicare Part D Drugs Selected for Inflation Reduction Act Drug Price Negotiation, for Price Applicability Year 2026
These 10 drugs represent roughly 20% of Medicare Part D drug spending

Brand Name	Generic Name	Drug Manufacturer	Conditions	2020 Medicare Part D Gross Drug Spending ($Billion)	2021 Medicare Part D Gross Drug Spending ($Billion)	Medicare Part D Gross Drug Spending from June 2022-May 2023 ($Billion)	Number of Medicare Part D Enrollees Using the Drug
Eliquis	Apixaban	BMS	Prevention and treatment of blood clots	$9.9	$12.6	$16.5	3,706,000
Jardiance	Empagliflozin	Boehringer Ingelheim	Diabetes; Heart failure	$2.4	$3.7	$7.1	1,573,000
Xarelto	Rivaroxaban	Janssen Pharma.	Prevention and treatment of blood clots	$4.7	$5.2	$6.0	1,337,000
Januvia	Sitagliptin phosphate	Merck Sharp & D	Diabetes	$3.9	$4.1	$4.1	869,000
Farxiga	Dapagliflozin Propanediol	Astrazeneca	Diabetes; Heart failure; chronic kidney disease	$0.7	$1.4	$3.3	799,000
Entresto	Sacubitril/Valsartan	Novartis	Heart failure	$1.2	$1.7	$2.9	587,000
Enbrel	Etanercept	Amgen	Rheumatoid arthritis; Psoriasis	$2.2	$2.4	$2.8	48,000
Imbruvica	Ibrutinib	Pharmacyclics	Blood Cancers	$3.0	$3.2	$2.7	20,000
Stelara	Ustekinumab	Janssen Biotech	Psoriasis; Psoriatic arthritis; Crohn's disease; Ulcerative colitis	$1.1	$1.6	$2.6	22,000
Fiasp; Fiasp FlexTouch; Fiasp PenFill; NovoLog; NovoLog FlexPen; NovoLog PenFill	Insulin Aspart (Niacinamide)	Novo Nordisk	Diabetes	$2.5	$2.4	$2.6	777,000
Total				$31.5	$38.2	$50.5	9,738,000

Source: CMS, BofA Global Research

BofA GLOBAL RESEARCH

Continued Legal Challenges to IRA Drug Price Negotiations - Manufacturers of the ten selected drugs have filed lawsuits challenging the drug price negotiation provisions of the IRA. Drug manufacturers highlight several Constitutional and administrative challenges to the law, including first amendment (free speech); fifth amendment (due process and uncompensated takings); eighth amendment (excessive fines); and Administrative Procedures Act issues. In AstraZeneca's case (filed in Delaware), the Judge has laid out a timeline that includes filings through early January, with oral argument targeted for January 31, and potential decision in March 2024. The other legal challenges may take longer to play out over the course of 2024.

Inflationary rebates for Medicare Part B and Part D – New inflationary caps took effect for Part D, for the 12-month period beginning October 1, 2022, with HHS notifying manufacturers of required rebates no later than 9 months after the end of this period (i.e., July 1, 2024). For Part B drugs, the inflationary caps took effect for each quarter beginning January 1, 2023, with HHS notifying manufacturers of the required rebate no later than 6 months after the end of each calendar quarter. However, HHS has noted that it can delay the reporting of Part B rebates for 2023 and 2024 until September 2025; and for the first two years of Part D rebates until December 2025.

HHS reports that for 2023, a total of 47 drugs had adjusted coinsurance rates based on inflation-adjusted payment amounts.

On December 14, CMS released revised guidance on the Medicare Part B and Part D drug rebate programs. The guidance provides additional detail on the calculation of rebates owed to Medicare for Medicare Part B and Part D drugs that exceed inflationary drug price increases. The revised guidance focuses on the determination of rebate reduction amounts for drugs in drug shortages, severe supply chain disruption, or likely to be in shortage, and reporting the 340B modifier for the Part B inflation rebates. CMS also released an updated list of 48 Medicare Part B drugs that triggered inflation rebates and will result in lower cost-sharing for beneficiaries in the 1st quarter of 2024. This is an increase from 34 Medicare B drugs subject to the inflationary rebates as calculated in in the previous quarter.

Potential Revisions to the Drug Price Negotiations in the Inflation Reduction Act

While we do not expect any significant changes to the Inflation Reduction Act's drug price negotiation provisions in 2024, as Senate Democrats and the Biden Administration have both made it clear that they will not negotiate over any significant revisions to the law, there may be opportunity for future modifications to the law in 2025 and beyond, depending on the outcome of the 2024 elections, and how smoothly the implementation of the negotiations proceed in 2024 and 2025.

We also note that Congressional Democrats and President Biden have proposed increasing the number of drugs that would be eligible for drug price negotiation under the Inflation Reduction Act, however, we do not see this effort gaining traction in a Republican House and have not seen any movement.

Drug manufacturers have also discussed a few potential areas for revisions in the law, including:

- **Equalizing the difference in treatment between small molecules and biologics.** The selection of drugs for negotiation begins 7 years after FDA approval (implementation after 9 years) for small molecules and begins 11 years after FDA approval (implementation after 13 years) for biologics. There have been proposals to equalize these timelines at the longer 11 years (13 years), however, those efforts have not yet gained traction in Congress. This distinction between 9 years vs. 13 years may lead to limitations in R&D for certain therapeutic areas, including cardiovascular disease or certain cancer treatments that target small molecule drugs.

- **Orphan drug exemption.** The IRA excludes orphan drugs from drug price negotiations, however, only for drugs with a single approved indication. The concern has been that drug manufacturers may be less likely to pursue additional indications for orphan drugs, and may impact research and development for certain rare diseases. Bipartisan legislation introduced in September would exempt all orphan drugs with multiple approved uses from drug price negotiation process.

- **Collection of Part B and Part D inflationary rebates.** Senate Finance Committee Chairman Wyden has called on CMS to speed up its collection of Medicare Part B and Part D inflationary rebates. Under current law, CMS has begun calculating Part B inflationary rebates since January 2023, and Part D rebates since October 2022. However, CMS has not made it clear when it will collect those rebates from drug manufacturers, noting that the law allows CMS to delay collections until 2025.

Healthcare Legislative Proposals

Congress continues to work on several key healthcare legislative proposals that include expanded transparency for several healthcare providers, including hospitals (that already are required to provide price transparency), ASCs, clinical labs, imaging, and health plans. Proposals also call for providers to disclose their ownership structures and vertical integration. Along with these efforts, there are several proposals targeting Pharmacy Benefit Managers (PBMs). The most common provisions that target PBMs call for increased disclosures and transparency by PBMs to their employer and managed care clients. Other common proposals call for a prohibition on Medicaid spread pricing contracts. Other proposals would further limit PBM activities, including "de-linking" PBM compensation from the cost of medications, allowing only administrative fees in Medicare Part D, or limiting rebates and other fees, but these efforts may be less likely.

On December 11, the House passed the Lower Costs, More Transparency Act, including a range of healthcare provisions. The package includes healthcare transparency provisions for hospitals, clinical labs, diagnostic imaging, ambulatory surgery centers (ASCs), and health plans. The bill also includes PBM transparency and semi-annual reporting requirements to include data on prescription drug spending, acquisition cost of drugs, total out-of-pocket spending, formulary placement rationale, and aggregate rebate information. Another provision would prohibit Medicaid spread pricing contracts for PBMs, and another provision would require Medicare Advantage plans to report any common ownership between health plans, PBMs and pharmacies. The bill also includes a modest site-neutral payment reform for hospitals, reducing Medicare payments to hospitals for physician-administered drug services. CBO estimates this site-neutral provision would reduce hospital Medicare payments by $3.7 billion over 10 years. The package also provides funding for community health centers for 2 years (at $4.4 billion per year), and delays Medicaid Disproportionate Share (DSH) hospital payment cuts for 2 years ($8 billion per year). Hospital groups including the American Hospital Association are supportive of much of the package but are opposed to the site-neutral payment provisions. With the House passing this package, it provides momentum for including a healthcare package as part of an upcoming Continuing Resolution, or Appropriations bill that must be passed by January 19 to avoid a partial government shutdown. We also note that the House and Senate continue to work on additional healthcare proposals to be part of the package, including 2024 Medicare physician payment relief, Medicare DME payment relief, PBM reforms, along with other Medicare cost-sharing, coverage, telehealth, and drug provisions.

Other drug-related proposals that have been discussed as part of a potential healthcare package in January includes:

- Generic drug proposals (transparency on quantitative differences).

- Increase biosimilar access (mid-year formulary changes).

- Limit cost-sharing for drugs in Medicare Part D by ensuring that patients would not pay more than the Part D plan is paying for highly rebated drugs

- Reduce Medicare Part D cost-sharing for generic drugs for low-income patients by setting generic co-pays at $0.

Senate HELP Committee Chair Sanders Calls for Additional Drug Pricing Legislation - We also highlight the continued focus on drug prices in Congress and by the Administration. Senate HELP Committee Chairman Bernie Sanders (I-VT) announced that a hearing on drug pricing issues, "Why Does the United States Pay, By Far, The Highest Prices In The World For Prescription Drugs?" and invited CEOs from invited CEOs from Johnson & Johnson, Merck, and Bristol Myers Squibb to testify. The hearing is expected to focus on the differential between drug prices in the US vs. prices in other countries for leading drugs. Senator Sanders has stated he plans to introduce legislation that would limit drug manufacturers from charging more in the United States than they do in certain other countries. Senator Sanders highlighted this potential approach to limiting drugs at hearing on diabetes and obesity. This proposal is similar to an earlier proposal from President Trump that would have limited Medicare Part B drug prices to an International Pricing Index (IPI). While we do not expect Congress to move forward on Senator Sanders proposal in 2024, it does remain a potent political issue.

Patent Reform and Generic Drug Legislative Efforts – We also highlight several patent reform and generic drug legislative proposals that have bipartisan support in Congress, and have passed in Committee, but, have not yet come to floor votes. These include efforts to limit "pay-for-delay" agreements by manufacturers, limits on "product hopping" and other tactics to limit generic introduction, limitations on use of citizen's petitions, and additional efforts to increase introduction of generics and biosimilars.

Medicare Coverage for Obesity Drugs

With the continued growth in utilization and development of GLP-1drugs, there continues to be significant attention on when/if Congress or CMS will revise Medicare policy to cover these drugs. Legislation that would allow for Medicare coverage of these drugs has been introduced in Congress over the last several years. Under current law, Medicare is prohibited from covering drugs if used solely for weight loss, (GLP-1 agonists are covered for the treatment of diabetes but not for the treatment of obesity.)

While there is bipartisan support for legislation to allow Medicare to cover these drugs, the Treat and Reduce Obesity Act (TROA) has not moved forward due to the potentially large cost to the government of providing coverage for these drugs in Medicare.

In October, the Congressional Budget Office (CBO) issued a request for additional research on the potential costs and savings related to Anti-Obesity Medications (AOMs). CBO highlighted recent trends in utilization of AOMs, noting, net U.S. sales of semaglutide (including Ozempic, Rybelsus, and Wegovy) in the second quarter of 2023 were $3.4 billion. Net sales of all GLP-1 agonists, which include other drugs known to reduce obesity, totaled $5.9 billion during that same period. CBO expects that the providing coverage for AOMs would result in significant net cost increases to the Medicare program over the next 10 years. CBO also stated that it expects semaglutide will be selected for drug price negotiation by HHS in the next few years, which would lower its price. CBO is still trying to better understand how increased use of AOMs by people with obesity (and who are not diabetic) could improve their health, and therefore reduce the utilization of healthcare services and lower federal spending for other types of health care over time. CBO stated that it would like to see new research on factors affecting their use, such as take-up rates, patients' adherence to drugs currently on the market, and expectations about the prices and effectiveness of AOMs that are being developed, and the near- and long-term clinical impacts of AOMs (including health benefits or complications associated with them) and their effects on patients' use of, and spending on, other medical services would also be of particular interest.

However, until CBO develops an estimate of the overall costs and benefits of providing Medicare coverage for AOMs, the legislation will be difficult to move through Congress.

Some members of Congress, including Senator Bill Cassidy (R-LA), ranking member of the Senate HELP Committee, have discussed other approaches to providing Medicare coverage for GLP-1s, including a hybrid long-term treatment of obesity starting with one year of coverage of GLP-1 drugs followed by dietary therapy and other options. Senator Cassidy has called on NIH to study this hybrid approach to coverage, which could be an alternative to keeping patients on the drugs for the remainder of their lives. Obesity advocates have endorsed similar approaches to help patients lose weight, and then use lower cost interventions to help maintain weight loss.

However, we also note payers and employers have also cited the potential long-term side-effects of GLP-1 drugs as a concern, and have also endorsed nutrition counseling as an alternative, or in conjunction with AOMs.

Another approach to providing coverage for GLP-1 drugs in Medicare would be for CMS to revise its coverage policy to interpret obesity as a chronic disease. If CMS were to revise its coverage policy, so that obesity treatment is not solely for weight loss then CMS could provide Part D coverage for AOMs as a treatment targeting obesity as a disease rather than just a weight loss therapy.

Overall, we continue to expect that Medicare coverage for GLP-1s will remain an issue for Congress and CMS over the next year, and ultimately, we do expect some movement towards providing coverage for these drugs in the next several years, particularly as utilization of GLP-1s continues to grow.

340B Drug Discount Program

The 340B Drug Discount program continues to grow in utilization, and has become a key issue for both participating entities (hospitals, clinics, and pharmacies), as well as for drug manufacturers who have seen the discount program grow from $38 billion in 2020 to $54 billion in 2022.

Congress created the 340B Program in 1992 for health care providers that serve low-income and uninsured patients to purchase drugs at lower costs. The 340B discount program is administer by the Health Resources and Services Administration (HRSA), but its regulatory authority over the program is limited. HRSA estimates that 340B sales represent 7.2% of the overall U.S. drug market and reports that in 2022, total program sales reached $54 billion, 22% increase over 2021. Drug manufacturers that participate in the Medicaid Program are required to offer outpatient drugs to “covered entities” at discounted prices. HRSA estimates that at least $470 million of the $53.7 billion total was comprised of purchases above the upper limit of discounted pricing, which represents discounts lost by providers due to restrictions imposed by drug manufacturers.

Over the last several years, drug manufacturers have challenged the expansion of the 340B drug discount program through litigation, as manufacturers imposed restrictions on covered entities that purchase 340B medications through contract pharmacies. Efforts by HRSA to clarify or regulate the program by issuing violation letters to manufacturers have been challenged in court, and those cases continue to make their way through appeals courts. We expect that these cases will continue to make their way through the courts in 2024.

In Congress there has been growing interest in the 340B drug discount program. In June 2023, a bipartisan group of Senate Finance Committee members issued a request for information on the 340B drug discount program seeking additional information on: HRSA’s oversight of the 340B program; Policies to address contract pharmacy arrangements for covered entities; Efforts to ensure 340B program benefits patients they serve, not other parties; Efforts to ensure duplicate discounts do not occur; and How best to improve the accountability of the 340B program?

In September, Senate HELP Committee Ranking Member Bill Cassidy (R-LA) opened an investigation into 340B drug discount program, with a particular focus on two not-for-profit hospital systems, Bon Secours, and the Cleveland Clinic. The Senator is reviewing "how certain hospital systems may spend revenue generated from the 340B Drug Pricing Program." Senator Cassidy also notes that his investigation "follows multiple reports of certain 340B recipients announcing record-setting profits with no transparency on if and how much of that profit benefits patients."

"The 340B Program is regularly reviewed by the Government Accountability Office (GAO) and HHS's Office of Inspector General (OIG), both of which have highlighted issues with the program," continued Dr. Cassidy. "GAO has identified the troubling recent pattern of 340B covered entities increasingly serving wealthier communities with higher rates of insurance, which is far afield from the program's intent. Additionally, GAO has found that covered entities often do not share 340B discounts directly with their patients."

In March 2023, Drug manufacturers, as well as some patient groups and health clinics created a new coalition proposing reforms to the 340B discount program, with PhRMA seeking more transparency in how 340B discounts are being used by hospitals, and efforts to ensure that patients benefit from the discounts provided. The coalition outlined 10 principles for reform in the 340B drug discount program.

We expect more discussion of 340B reforms in 2024, but, not expect any major legislative action in 2024.

Regulatory Issues for 2024

CMS and FDA continue to focus on a range of regulatory and payment ssues. We highlight several of the key regulatory efforts that will continue to be developed and may be finalized in 2024:

- **Drug pricing – March-In Rights -** On December 7, the Administration released its draft guidance implementing a new framework to use March-In Rights for drugs. The Request for Information (RFI) on the new guidance would assist agencies on policy considerations when considering using march-in authority for patents that were developed from government or NIH research. The Administration will accept comments through February 6, and will address stakeholder comments before finalizing the guidance. The use of March-in Rights for drug pricing remains controversial, and we would expect that the Biden Administration will remain cautious in finalizing this guidance and implementing any new authority in 2024.

- **FTC-DOJ Merger Guidelines –** On December 18, the FTC and DOJ issued its 2023 Merger Guidelines, which describe factors and frameworks the agencies utilize when reviewing mergers and acquisitions. The revised merger guidelines "emphasize the dynamic and complex nature of competition ranging from price competition to competition for the terms and conditions of employment, to platform competition." The agencies expect to include a continued focus on healthcare mergers and acquisitions, and the new guidelines note "excessive market consolidation across industries and overwhelmingly urged the agencies to strengthen their approach to merger enforcement." We expect that healthcare services, and pharmaceuticals will remain a focus for FTC merger reviews into 2024.

- **FTC Orange Book Enforcement on Drug Patents –** In November, the FTC announced that it was following through on its recent policy statement to address improper or inaccurately listed patents on FDA's Orange Book list, and specifically announced that it was challenging 100 patents listed in FDA's Orange Book. The FTC also sent letters to 10 drug manufacturers citing specific patents that they claim were improperly listed for specific asthma and other inhaler devices, Restasis multidose bottles, and epinephrine autoinjectors, also commonly known as EpiPens. Manufacturers then had 30 days to withdraw or amend the patent listings, or certify under penalty of perjury that the listings comply with applicable statutory and

regulatory requirements. FDA Commissioner Califf stated that he supports FTC effort to protect consumers from improperly listed patents in the Orange Book.

- **Biosimilar Interchangeability –** In September, FDA issued draft guidance to remove labeling distinctions between interchangeable and biosimilar products. The new guidance could help spur additional utilization of biosimilars, and help patients and providers understand that biosimilars are safe and may be interchangeable with reference biologics. Specifically, the new guidance notes that biosimilar labels do not have to include clinical data to establish biosimilarity, and no need for an interchangeability statement.

2024 Elections Impact on Health Policy

As we head into an election year in 2024, we expected that healthcare will once again play a significant role. We expect that President Biden will look to highlight healthcare and his achievements as part of his campaign, including the following key issues:

- **Inflation Reduction Act –Drug Pricing Reforms –** We expect that President Biden will campaign on the Inflation Reduction Act, and with the first 10 drug price negotiation final results being announced in August/September, this will certainly be a highlight for the President heading into the fall campaign.

- **Proposals to Expand number of Medicare Drugs to be negotiated –** President Biden has also proposed increasing the number of drugs subject to drug price negotiations. While this may be a talking point for the campaign and some Democrats in Congress, we do not see much likelihood of this happening in the next several years.

- **Extend savings to Commercial Drugs –** President Biden has also highlighted proposals to extend drug pricing reforms beyond Medicare drugs to commercial and extend out-of-pocket caps on insulin products to commercial plans as well. While there is bipartisan support in Congress for extending the insulin out-of-pocket cap, we do not expect much traction on these proposal in Congress this year.

- **Recent Proposals on "March-In Rights"** on drugs developed with NIH Research ♣ FTC Efforts and Focus on Consolidation and Competition

- **Orange Book Challenges to listed drug patents** – We expect that FTC will continue to pursue these Orange Book challenges into 2024.

- **Increased scrutiny on healthcare mergers and consolidation / New Interagency Counsel on Health Care Competition**

- **Extend ACA Enhanced Premium Subsidies Beyond 2025 –** Under current law, the enhanced premium subsidies for health insurance exchange plans will expire at the end of 2025. We expect that Democrats will look to extend or make permanent these enhanced subsidies. However, we expect opposition from Republicans in Congress, setting up negotiations on the subsidies in 2025, pending the outcome of the elections.

- **Provide Coverage for Individuals in Medicaid Coverage Gap** – President Biden has noted that he would like to make additional progress on providing coverage for individuals in the Medicaid coverage gap in 10 states. While there may be some regulatory actions President Biden can take, we do not expect any additional legislative efforts on providing additional incentives for states to expand Medicaid. We note that North Carolina became the latest state to expand Medicaid on December 1 (600K individuals).

Therapeutic Themes

We've highlighted what we view as the most impactful therapeutic areas in 2024, both in terms of clinical progress and commercial/ regulatory dynamics. We expect these areas to not only be important from a company-specific perspective given the importance of some of these therapies for their respective growth narratives, but they also may become focal points for M&A activity over the next 12-18 months as larger players look to expand their capabilities and/or presence in new areas.

In this section we'll be taking a deeper look our view of the top 4 therapeutic themes heading into 2024, which we've identified as the following (including our affiliated companies):

1. **Obesity therapeutic landscape + label expansion opportunities**: We've seen investors acutely focused on the clinical and commercial opportunities for obesity and potential label expansion opportunities in 2023 and we don't expect this momentum to change in 2024. Indeed, while the treatment landscape for Type 2 diabetes and obesity is currently a duopoly, we've seen a number of new entrants in 2023 as both investors and the broader healthcare space have recognized how meaningful the commercial opportunity could be. Moreover, we wouldn't be surprised to see even more players get into the space in 2024 (potentially though M&A), especially as we should have a clearer line of sight into 1) access + reimbursement and 2) persistence of use.
2. **Pain:** Given Vertex's recent success with NaV1.8 inhibitor, VX-548, we expect to see a resurgence of interest in non-opioid pain assets from both Pharma and Biotech alike in 2024, especially if Vertex's phase 3 acute pain results, expected in early 2024, are favorable. Moreover, while precedent highlights that pain can be painful, investors recognize the commercial opportunity in pain, particularly in neuropathic pain given the potential for chronic dosing, so we expect to see increased innovation in the space as investors look for new therapeutic areas to get excited about. That said, there's still more work to do when it comes to access + reimbursement, as generics are heavily entrenched in both acute + neuropathic pain, with some investors arguing that congressional acts such as the No Pain Act will need to be further broadened for the commercial opportunity to inflect.
3. **Antibody-drug conjugate (ADC):** 2023 had been a very busy year for ADCs, with multiple acquisitions/collaborations (e.g., Pfizer/ Seagen, AbbVie/ Immunogen, Merck/ Daiichi, and Bristol/SystImmune) and important data readouts (e.g., Padcev's EV-302, Elahere's MIRASOL, Dato-DXd's TROPION-Lung01/Breast01, and Trodelvy's Evoke-02). We expect interests in ADCs to remain elevated in 2024, especially in hard-to-treat cancers where IO-based regimen hasn't found much success as well as IO/ ADC combo regimens in front-line setting, where we expect to see incremental data updates and continuous debate on the which ADCs will likely reign over the crowded market, becoming the next Keytruda/Opdivo/Tecentriq.
4. **Inflammation & Immunology**: JAK/STAT inhibitors are being investigated for the treatment of "second-generation" I&I markets, including lupus, alopecia, and vitiligo. Despite the flurry of clinical developments in these indications over the last few years, our deeper dive on the treatment landscape reveal disease-specific challenges. That said, we do think approval in one or more of these underpenetrated I&I markets could provide tailwinds for the battered JAKi class. Our primary takeaways on the outlook of these markets are: 1) while we recognize the high unmet need in SLE, we remain cautious on the opportunity given the high clinical trial failure rate, 2) we think the market opportunity in alopecia areata could be substantial and uptake among severely affected individuals will likely be robust, and 3) treatment needs in vitiligo are unclear, though efficacy of systemic biologics for vitiligo treatment is remarkable.

1) Obesity: Clinical and commercial progress with potential for label expansions

Obesity has historically been characterized as a "lifestyle disease" versus a chronic medical condition and while we've made great progress on more efficacious and safe therapies, the stigma of obesity is still present, in our view, leading to commercial hurdles (e.g., access). That said, we think Lilly and Novo (covered by Sachin Jain and Graham Parry) have done a good job implementing a "back door strategy" whereby the companies are focusing on weight-related comorbidities (e.g., chronic kidney disease (CKD), obstructive sleep apnea (OSA), and Nonalcoholic steatohepatitis (NASH)) with established reimbursement pathways to increase access + reimbursement as we await either 1) approval of the Treat and Reduce Obesity Act (TROA, a bipartisan bill which allows CMS to expand Medicare Part D coverage to include FDA-approved anti-obesity medications (AOMs)) or 2) expanded commercial access through employers. Nevertheless, even with these hurdles, investors have acknowledged the commercial opportunities for obesity and the potential label expansions into additional weight-related comorbidities, which we expect to continue driving innovation across the sector.

What are we expecting for access + reimbursement in 2024?

We would say that limited access + reimbursement remains by far and away the biggest overhang in the obesity space currently. That said, having two large pharma companies working to expand access creates a favorable backdrop, in our view, though based on our channel checks, we still suspect it will take a few years until we see access as broad as we do for Type 2 diabetes. But given the supply constrained environment for parenteral manufacturing of Lilly's tirzepatide and Novo's semaglutide, we see supply as an equally limiting factor than access in the near-term (see below). In terms of next steps for access + reimbursement, we'd highlight 1) TROA, 2) commercial access through employers (currently as ~50%) and 3) flexible pricing. See our thoughts below on the likelihood of each.

1. **TROA and Medicare coverage**- Currently, the major limitation for broad access + reimbursement is the lack of Medicare coverage, given most commercial payers follow Medicare for reimbursement decisions. However, our key opinions leaders (KOLs) have been clear in their agreement that TROA, a bipartisan bill which allows CMS to expand Medicare Part D coverage to include FDA-approved anti-obesity medications, is unlikely to pass Congress in its current state. To put TROA into a broader context, it was first introduced into the 113th Congressional session in 2013 and has been reintroduced in every subsequent Congress since the 113th session (currently in the 118th session). While there is bipartisan support, our KOLs suspect the price tag for TROA could be a tough pill to swallow (>$50B) but increasing the barriers for treatment under the act could improve the likelihood of approval (e.g., BMI ≥35kg/m² with comorbid conditions vs. Lilly's Zepbound or Novo's Wegovy inclusion criteria of Body Mass Index (BMI) ≥27kg/m² in the presence of at least one weight-related comorbid condition). Indeed, the biggest hurdle to TROA remains a potential Congressional Budget Office score for the bill which has not yet been released. According to Andy Bressler, our DC Policy expert, the CBO is still working to score TROA as they've put out a request for more research on the issue, likely following Novo's pivotal SELECT results (see our initial thoughts on SELECT here and post a KOL call here). Notably, there has been a movement by some in Congress to "direct" CBO to score the bill as a savings– as some Academic research suggests there could be meaningful savings for Medicare if obesity is reduced due to lower diabetes and heart disease. However, a New England Journal of Medicine (NEJM) article in the spring said if 10% of eligible Medicare patients received semaglutide, it would cost $27B or 18% of Part D net spending, so there is clear debate over the cost-benefit analysis. Ultimately, we suspect TROA will be more of an issue over the next 1-2 years –especially if an increased number of commercial plans begin paying for Zepbound and Wegovy, as this would pressure Medicare to cover them as well. Importantly, there has been progress on the access

front at the Federal level, including health plans for federal employees with many large corporations also following suit and covering obesity care beginning in 2023.

2. **Commercial access through employers**- As Lilly's Zepbound was only recently approved (see our thoughts on Zepbound approval here), we look to Novo's Wegovy to set precedent for what commercial access looks like for anti-obesity medications (AOMs). According to Novo, there are ~110M obese adults in the US, with ~60M patients in the commercial channel. Novo has received >80% formulary access for these commercial patients, with >50% employer opt-in, which means ~38M people with commercial coverage have access to Wegovy. And while Medicare doesn't cover AOMs, there are at least 16 States which cover at least one form of AOM, but not necessarily the glucagon like peptide-1's (GLP-1s) as of July 1st, and Novo has said that ~12M patients have access through this route. Altogether, this means that ~50M patients have access to Wegovy in the US and importantly, 80% of these patients are paying no more than $25 a script ($1,350 gross) as of Novo's 3Q23 earnings call, which speaks to Novo's heavy rebates. However, there are less than 1M patients on Wegovy currently, so while 50M US patients have access clearly there is a bifurcation between commercial access + use which will have to improve moving forward. That said, we suspect that use + employer opt-ins will improve with consumers + employees demanding clearer guidelines and reimbursement, similar to what happened in the mental health space 10 years ago (see our note on the importance of online platforms here). Moreover, with Lilly in the process of launching Zepbound for obesity as well, we expect a ramp as Lilly's commercial arm works with payers and employer opt-ins with a focus on broadening coverage and improving patient use with favorable gross-to-net dynamics. But we don't expect the launch to be as robust as Wegovy's relaunch in 2022, as Lilly's management has reiterated that it doesn't have the infrastructure in place as Novo did. We also wouldn't be surprised if these negotiations focused on patients with higher BMI and a higher number of comorbidities, as these patients in particular drive the cost-effectiveness of AOMs given they patients are most at risk for comorbidities. To this point, as of 3Q earnings, Novo highlighted Wegovy patient characteristics in the US as follows 1) 77% of patients are new to an AOM, 2) 81% of patients are female, 3) the average BMI is 37.5 kg/m², and 4) 30% of patients have ≥3 comorbidities, which further supports this hypothesis.

3. **Flexible pricing**- While Novo's Wegovy has a gross price of $1,350 per month, Lilly's Zepbound is $1,060 per month- a >20% discount, which we think investors, prescribers, patients, and payers viewed favorably. However, there's still more work to do, with UNH (covered by Allen Lutz) noting during its 3Q call that "we're really trying to work with manufacturers to get to some aligned value-based constructs. Getting pricing to a point where it's based on outcomes and adherence levels, all the way to outright risk on utilization levels and pairing those with therapies and programs that can put less reliance on lifelong adherence requirements like these drugs currently have. We're not there yet. We're optimistic that we can get there. But clearly, price point is a key barrier." To this point, Novo's CEO Lars Fruergaard has said that while Novo doesn't plan to lower the cost of Wegovy, it's looking into flexible pricing models "to make it possible to adopt medicines upfront, see the benefits and pay down the road", like a warranty or outcome-based agreement (OBA) that we've seen for some curative intent gene therapies (e.g., BioMarin's Roctavian). We think this strategy makes a lot of sense particularly given patients usually change employer insurance plans every 3-4 years which makes the return on investment (ROI) less favorable, particularly in light of the 3-years it took to see cardiovascular benefits with Wegovy in Novo's SELECT trial.

Label expansion could provide additional leg of growth for GLP-1's

While we wait for AOM access + reimbursement to expand the traditional way (see above), Lilly and Novo have a backdoor reimbursement strategy for both Zepbound and Wegovy, respectively, that could provide the assets next leg of growth. Indeed, the Venn diagram of overlapping diseases is quite robust, including cardiovascular disease (CV), CKD, OSA, osteoarthritis, Alzheimer's disease, Heart failure with preserved ejection fraction (HFpEF) and eye disease to name a few, which overall have relatively straightforward reimbursement pathways (see Exhibit 40). So, we think it makes a lot of sense that Lilly and Novo are targeting these indications, as if Zepbound and Wegovy receive approval, patients would have another way to access AOMs for obesity. Moreover, given the Venn diagram of overlaps of obesity with other metabolic conditions, it wouldn't be surprising if weight loss improves a wide range of metabolic conditions, further opening the gate for access.

To demonstrate the importance of this strategy, we'd highlight Novo's SELECT trial with Wegovy, which was arguably the biggest catalyst in the space in 2023. We've received in-depth results for Novo's Wegovy SELECT trial at the American Heart Association conference this past fall, which we thought was best case scenario from a cost effectiveness perspective as on the primary composite endpoint, the risk of CV death, myocardial infarction (MI), or stroke, was reduced by 20% (Hazard ratio (HR): 0.80; p<0.001). Notably, there was early separation of the curves before weight lost occurred, supporting the in-direct effects of GLP-1 agonists likely due to improvements in blood pressure. Indeed, the absolute risk reduction was 1.5% (in-line with expectations), with the number needed to treat (NNT) to prevent one event, 67 patients. To put this in context, in a meta-analysis of 8 trials looking at GLP-1s in patients with CVD+T2D, there was a 14% reduction in CV death, non-fatal MI, and non-fatal stroke, with a NNT of 65, a marginal difference, in our view, and supportive of broad access + reimbursement for GLP-1s in overweight/ obese patients with CV risk. As highlighted above, these results further add to the cost-effectiveness discussion to increase access + reimbursement, adding to the burden of proof of the benefits of AOMs.

In terms of upcoming catalysts, we'd highlight for Lilly we should receive phase 2 results for tirzepatide in NASH in 1Q24 and phase 3 results for Sleep Apnea in 2Q24 + HFpEF in mid-2024, which we expect to keep investors engaged looking to 2025 when we should receive pivotal results for Lilly's next-generation assets oral orforglipron and triple-G retatrutide. For Novo, we should receive detailed phase 3 FLOW CKD data in early 2024 (recall Novo discontinued the trial due to efficacy) and phase 3 results in peripheral arterial disease (PAD) in mid-2024 + phase 3 results in eye disease in 2H24. Overall, we expect these catalysts to not only keep the GLP-1 momentum alive, but also provide additional upside to the Street's forecasts and therefore potentially provide GLP-1's next leg of growth.

Exhibit 40: Ongoing clinical trials for label expansion opportunities
The multitude of ongoing trials underscores Lilly + Novo's bullishness for the commercial opportunity

Company	Drug	Trial Name	Indication	Phase	Study Size (pts)	Primary Outcome	Timing
Lilly	tirzepatide	SURMMOUNT-MMO	Obesity	3	15,000	Time to First Occurrence of Any Component Event of Composite (All-Cause Death, Nonfatal Myocardial Infarction, Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events)	2027
Lilly	tirzepatide	SURPASS-CVOT	T2D	3	13,299	Time to First Occurrence of Death from Cardiovascular Causes, Myocardial Infarction or Stroke (MACE-3)	4Q24
Lilly	tirzepatide	SYNERGY-NASH	NASH	2	196	Percentage of Participants with Absence of NASH with no Worsening of Fibrosis on Liver Histology	1Q24
Lilly	tirzepatide	SURMOUNT-OSA	Sleep Apnea	3	469	Percentage Change from Baseline in Apnea-Hypopnea Index	2Q24
Lilly	tirzepatide	SUMMIT	HFpEF	3	700	A Hierarchical Compositive of All-Cause Mortality, Heaty Failure Events, 6-minute Walk Test Distance	Mid-24

Exhibit 40: Ongoing clinical trials for label expansion opportunities
The multitude of ongoing trials underscores Lilly + Novo's bullishness for the commercial opportunity

Company	Drug	Trial Name	Indication	Phase	Study Size (pts)	Primary Outcome	Timing
						and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score Category	
Lilly	tirzepatide	TREASURE-CKD	CKD	2	140	Change from Baseline in Kidney Oxygenation in Participants With or Without T2D	1Q26
Lilly	retatrutide	-	CKD	2	120	Change from Baseline in Glomerular Filtration Rate (GFR)	4Q25
Lilly	retatrutide	TRIUMPH-4	Knee osteoarthritis	3	405	Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score	2026
Novo	semaglutide	SELECT	Obesity	3	17,500	Cardiovascular risk reduction with respect to reducing the incidence of MACE (a composite primary endpoint consists of: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	Further subgroup analysis-2024
Novo	semaglutide	STEP-HFpEF	HFpEF / Obesity	3	516	Change in Kansas City Cardiomyopathy Questionnaire score and percentage change body weight	Readout at ADA
Novo	semaglutide	STEP HFpEF DM	HFpEF/ Obesity / T2D	3	610	Change in Kansas City Cardiomyopathy Questionnaire score and percentage change body weight	2H'23
Novo	semaglutide	SMART	Obesity / CKD	3	98	Change from baseline to week 24 in urinary albumin:creatinine ratio in individuals at high risk of CKD progression	2024E
Novo	semaglutide	REMODEL	CKD / T2D	3	105	Change from Baseline in Kidney Oxygenation in Participants With T2D	2024/2025
Novo	semaglutide	FLOW	CKD / T2D	3	3,508	Time to first occurrence of a composite primary outcome event defined as persistent eGFR decline of greater than or equal to 50 percentage from trial start, reaching ESRD, death from kidney disease or death from cardiovascular disease in Participants With T2D and CKD	1H24
Novo	semaglutide	ESSENCE	NASH F2-F3	3	1200	Count of Participants with resolution of steatohepatitis with no Worsening of Liver Fibrosis	End 2024/2025
Novo	semaglutide	STRIDE	PAD / T2D	3	800	Change in maximum walking distance on a constant load treadmill test in Participants With T2D and PAD	Mid-2024
Novo	semaglutide	FOCUS	T2D / Eye disease	3	1500	Presence of at least 3 steps Early Treatment Diabetic Retinopathy Study subject level progression	2H24
Novo	semaglutide	-	Knee osteoarthritis	3	407	Change in WOMAC pain score [Time Frame: From baseline (week 0) to end of treatment (week 68)] Score points	4Q23
Novo	oral semaglutide	SOUL CVOT	T2D / Heart disease	3	9,642	Time to first occurrence of a major adverse cardiovascular event (MACE), a composite endpoint consisting of: cardiovascular death/non-fatal myocardial infarction/non-fatal stroke	2024
Novo	oral semaglutide	EVOKE	Early Alzheimer's	3	1840	Change in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) score	2025
Novo	CagriSema	-	CKD	2	618	Change in urinary albumin-to-creatinine ratio (UACR) [Time Frame: From baseline (week 0) to end of treatment (week 26)]	4Q25

Source: BofA Global Research, Company Reports, Clinicaltrials.gov, PAD: peripheral artery disease, ESRD: End-Stage Renal Disease

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Supply constraints remain a challenge, but Lilly and Novo are making progress

Unsurprisingly, supply constraints—along with access + reimbursement— remains one of the top discussion themes in relation to AOMs. While we know Lilly and Novo are investing heavily to increase supply both in the near- and long-term, we still don't know the cadence of how quickly manufacturing from these facilities will come online, which creates a challenging backdrop for investors, in our view. All we know for certain is the demand far outstrips supply and we don't expect any changes in the immediate near-term.

That said, we'd argue that Lilly has made good progress as management continues to make investments in core manufacturing facilities. Importantly, Lilly is focusing not only parenteral manufacturing (e.g., pen presentations), but also manufacturing of the active pharmaceutical ingredient (API) of its incretin franchise, see below for Lilly + Novo's recent investments (Exhibit 41). Indeed, Lilly has heavily invested in two sites in North Carolina, one in Research Triangle Park (RTP) and one in Concorde, with the RTP site already ramping commercial production (initiated in 2Q23) and the Concorde site expected to start commercial production in 4Q23. Lilly is on track to double its incretin capacity with the RTP site alone, with the expectation that the ramp in capacity will turn into production of Mounjaro + Zepbound in 2024, providing a regular influx of updates as new lines start production. Recall, every line requires process validation, regulatory approval, and optimized production, so this process is labor + cash intensive. In addition to adding new lines, Lilly is also developing new presentations of tirzepatide, such a single vials, that have already been launched in Australia and Canada, reducing the parenteral capacity constraints. Lilly expects to continue to launch single vials outside the US, which will serve as a bridging into multi-dose Kwikpens (expecting approval in 2024) further highlighting how Lilly is diligently working to increase manufacturing capacity in an "all hands-on deck" manner.

Exhibit 41: Lilly + Novo have made significant investments in CapEx in the past year
Lilly + Novo investments in manufacturing in the past year

Company	Date	Location	Cost	Timing	Comments
Novo	Dec-23	Ireland	$92.5M	Mid-2024	Acquiring Alkermes' GMP facility
Novo	Nov-23	France	$2.3B	2026-2028	Increasing manufacturing capacity by extending the current quality control laboratory, adding aseptic production, and finishing production processes
Novo	Nov-23	Denmark	$6B	2025-2029	Expanding API production of existing plant, the new API facility will have a footprint of 170,000 m^2
Novo	Jun-23	Denmark	$2.3B	2029	Expanding API production of existing plant, the new API facility will have a footprint of 65,00 m^2
Lilly	Nov-23	Denmark	$2.5B	2027	To expand global parenteral (injectable) product and device manufacturing network, with gradual ramp overtime
Lilly	Apr-23	Indiana	$1.6B	-	To expand manufacturing for API of existing LEAP Innovation Park for a total commitment of $3.7B
Lilly	Jan-23	North Carolina	$450M	-	Expansion includes additional parenteral filling, device assembly and packaging capacity

Source: BofA Global Research, Company Reports

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Quotes from Lilly management below:

"While parenteral capacity has been the most immediate need from a supply standpoint, we are also thinking ahead to bolstering API capacity to support the incretin market over time. We generally don't speak to specific product manufacturing strategy, but I can say we have invested in bringing on additional API capacity to support our overall portfolio, including investment in a new $3.7M facility just north of Indianapolis to support API and new modality manufacturing. Across manufacturing, we preferentially invest internally, but also use external capacity to supplement where we can."

"This new [German] facility will expand our parenteral product and device assembly network. We expect it to be operational in 2027 with gradual ramp to occur over time."

"We haven't commented on like unit volumes per site. And so what we did say, though, was sort of a doubling of capacity potential with the North Carolina site coming on. Of course, capacity is not exactly the same as supply and we've got to work into that to produce it.

And that's just one stage of the process that we're talking about. The North Carolina site is a large site that is coming up in stages, as you suggested. And over the course of the next couple of years, actually, it'll continue to improve in its capacity potential."

"I'm quite confident that we can find bottlenecks anywhere in the supply chain for incretins, whichever one we sell first and the next one becomes equally important to sell. So we're working to increase capacity against all three aspects of manufacturing, which is API, the sterile fill, and the device manufacturing."

"So, I think in terms of Research Triangle Park (RTP), we are absolutely on track with the part that we committed to or announced back in late 2022 to double our capacity. And now in 2024, we will see that ramp-up of capacity turning into production and supplying the marketplace from RTP... So, we have invested heavily in our current site as well to upgrade those. We've taken other investments to support supply of incretins. And those efforts will continue in 2024. And the third component is while we have a preference for our own supply chain, just to control supply and quality at time of launches and years after launch, we also partnered with contract manufacturers and that will be -- continue to be the case for Tirzepatide as well. So those are three important components taking into account. And lastly, our efforts to develop new presentations for Tirzepatide. And we announced earlier this year that we have got the approval and launched Mounjaro in single vials in Australia and Canada, and that has been very well received. We plan to continue to launch single vials outside of the U.S. as a bridging into a multi-dose quick pen, which we expect to get approval for in 2024."

Persistence of use remains an open question, but we could get clarity in 2024

We've touched on access + reimbursement, supply constraints and finally, the last major theme in AOMs is persistence of use— do patients really need to be on these therapeutics chronically? Lilly has postulated that AOMs "are chronic medicines and are not intended for patients to go off therapy when they achieve their HbA1C (Hemoglobin A1C) or weight loss goal", however— given the high price, insurance coverage restrictions, and potential for side effects, investors have questioned this sentiment. Indeed, we currently model that patients will remain on therapy for only 9 mos and then patients will likely take a "drug holiday" as we've heard that some insurance companies who cover AOMs have strict guidelines to limit use, including 1) having to lose >5% of weight a month or 2) only covering the therapeutics for 1 year, which we expect to limit chronic use of these treatment. However, we expect that once patients regain some of the weight, they will cycle back on therapy, perpetuating a paradigm whereby patients get on and off drug every couple of years. That said, in Lilly's SURMOUNT-4 trial that looked at weight maintenance post tirzepatide use, once patients stopped therapy "much of their initial improvement in cardiometabolic risk factors had been reversed," which speaks to the benefits of chronic use. Prescribers we've spoken to have been split on the manner, see below for quotes on both sides. However, we could get some real-world clarity in 2024 with Wegovy being on the market for two years and Zepbound about a year, but supply constraints could confound any data points we may see.

Quotes supporting chronic use:

"The insurance companies that cover these medications are pretty aware that they need to be prescribed indefinitely, but only 20%–30% of private insurers are covering our agents, so many are not covering it, and neither is Medicare or Medicaid. And do you think that has something to do with the fact that it is chronic in nature? I mean, it's ridiculous that they cover hypertension medications, etcetera, which is a similar thing. And they're not covering obesity. But do you think that part of it, just like the chronic nature of these type of drugs, it's not a cure all or a complete, I should say? No, no. They're just they are just looking short term at the expense, which is $1,500 a month. And if you were an insurance company."

"And in terms of pharmacotherapy, we don't have a single option that either has any evidence supporting or has any reason to believe based on mechanism that any that initial weight loss, assuming stopping the medication would lead to any persistence of benefit. And

several studies have actually confirmed that where when patients are taken off the medications, they fairly rapidly regain weight. So, this is a chronic condition and pharmacotherapy short of something miraculous that comes out in the near future that's developed in the near future. Pharmacotherapy needs to be continued long term. So, there's no question about that."

"There's no question that this is a chronic condition and there is no reason whatsoever to believe with any of the medications or other treatments, even bariatric surgery that we have currently and with any of the medication treatments that are in development, there's no reason to believe that any of these things cure the problem or solve the problem and don't need ongoing management."

"Obesity absolutely fits the criteria of what a chronic disease is, and therefore, how a chronic disease should be approached."

"They're supposed to be used chronically, the same as Ozempic for diabetes. We use Wegovy the same way for obesity. But in clinical practice what we see is most patients started on the medications, unfortunately either because of cost or access or lack of efficacy. I can tell you that I have a bunch of people on Wegovy. And almost nobody has stopped it. Usually if they stopped it, it was because it was too strong. So, I do think that we're going to get patients on these medications chronically. We got to get the right people on them. You're correct. There's going to be a massive demand for these drugs by people in the lower BMI categories. And it's very hard to manage that as a physician."

"And patients who don't stay on drugs are unlikely as a result to derive those key benefits. I think actually for a community cardiologist it's a cost benefit trade-off."

Quotes supporting cycling of therapy:

"Many patients want and appreciate a drug holiday and don't seem to be that damaged by a drug holiday. And in fact, the weight loss is progressively beneficial if once they resume treatment and the experience of resuming treatment is as nearly as challenging as the first time as they took the medicine, they seem to retain some of the tolerability that they've built up over time in exposure to these agents."

Obesity is becoming a crowded area with new entrants

While obesity and Type 2 diabetes currently remains a duopoly with Lilly and Novo, there has been a slew of new entrants given investor interest in the space + the unprecedented total addressable market (TAM). That said, there has been a multitude of mixed results this year with Pfizer's two assets and some smaller players (e.g., Structure therapeutics and Altimmune) that underscore the clinical challenges of the space. Regardless, we expect the number of entrants to continue to swell beyond the >15 companies currently, especially we see progress on access + reimbursement (Exhibit 42).

Exhibit 42: Obesity Competitive Landscape
There are multiple new entrants to the obesity space

Company	Drug	MoA / Target	Development Stage	Admin	Catalyst
Agentix Corp (AGTX)	AGTX-2004	CB1 (cannabinoid receptor 1) antagonist	IND- enabling	Oral	TBD
Altimmune Inc (ALT)	Pemvidutide (ALT-801)	GLP-1/glucagon dual receptor agonist	Phase 2	SC, once- weekly	Phase 2 end of trial discussion with FDA; looking for partner to initiate phase 3
Amgen (AMGN)	AMG133	Multispecific GIPR antagonist/GLP-1 receptor agonist	Phase 2	SC, once monthly	Results 2H24
Amgen (AMGN)	AMG786	Undisclosed (non incretin-based therapy)	Phase 1	Oral	Results 1H24
Amgen (AMGN)	-	Multiple preclinical programs including non-incretin and GLP/GIPR-based mechanisms	Preclinical	-	"Advancing to the clinic"
AstraZeneca (AZN) + Eccogene	ECC5004	GLP-1 receptor agonist	Phase 1	Oral	Phase 1 results in management's hands by

Exhibit 42: Obesity Competitive Landscape
There are multiple new entrants to the obesity space

Company	Drug	MoA / Target	Development Stage	Admin	Catalyst
					2023; Phase 2 planned 2024
AstraZeneca (AZN)	AZD6234	Long acting amylin	Phase 1	SC/ IV monthly	Primary completion October 2023
AstraZeneca (AZN)	AZD9550	GLP- receptor and glucagon agonist	Phase 1	SC, once weekly	TBD
Lilly (LLY)	Zepbound	Dual GIP/GLP-1 receptor agonist	Approved	SC, once weekly	*see outcomes table
Lilly (LLY)	Orforglipron (LY3502970)	GLP-1 receptor agonist	Phase 3	oral, once daily	Enrolling pts; primary completion 2025/2026
Lilly (LLY)	Retatrutide (GGG agonist)	GIP/GLP-1/glucagon receptor agonist (GGG tri-agonist)	Phase 3	SC, once weekly	Enrolling pts; primary completion 2025/2026
Lilly (LLY)	DACRA QW II	Dual amylin and calcitonin receptor agonist (DACRA)	Phase 1	SC	Primary completion March 2024
Lilly (LLY)	Nisotirostide	Peptide YY activator	Phase 1	SC	Primary completion Nov 2023
Lilly (LLY)	Amylin agonist LA	Long acting amylin agonist targeting islet amyloid polypeptide (amylin)	Phase 1	SC	Primary completion Aug 2024
Lilly (LLY)	Bimagrumab	Binds activin type II A and B receptors to block activin and myostatin signaling	Phase 2 complete	IV	Primary completion May 2024
Lilly (LLY) / Innovent (IVBXF)	mazdutide (IBI-362)	GLP-1/ glucagon receptor agonist	Phase 3	SC, once weekly	Primary completion Jan 2024; Launch late 2024/ early 2025
Hanmi Pharmaceuticals (KRX: 128940)	LAPSGlucagon Combo (HM15136 +efpeglenatide)	Combination of a long-acting glucagon analog (HM15136; glucagon [GCC] agonist) and an exendin-4 analog (efpeglenatide; GLP-1 agonist)	Preclinical	-	TBD
Novo (NVO)	semaglutide	GLP-1R agonist	Approved	SC, once weekly	*see outcomes table
Novo (NVO)	oral semaglutide 50 mg	Long acting GLP-1 analog	Phase 3	Oral	Submitted in the EU; launch dependent on manufacturing; Phase 3 OASIS 4 results
Novo (NVO)	CagriSema	Combination of amylin analog (cagrilintide) + GLP-1 analog (semaglutide)	Phase 3	SC, once weekly	Primary completion December 2024* see additional table
Novo (NVO)	PYY 1875	Novel PYY analog (appetite-regulating hormone)	Phase 2 complete	SC, once weekly	TBD
Novo (NVO)	High Dose semaglutide	GLP-1 receptor agonist	Phase 3	SC, once weekly	Primary completion Oct 2024; NCT05649137
Novo (NVO)	High Dose semaglutide (STEP UP)	GLP-1 receptor agonist	Phase 3	SC, once weekly	Primary completion Sept 2024
Novo (NVO)	Subcutaneous amycretin	GLP-1 + amylin dual agonist	Phase 1	SC, once weekly	TBD
Novo (NVO)	Oral amycretin	GLP-1 + amylin dual agonist	Phase 1	Oral, once daily	Early 2024
Novo (NVO)	Oral amycretin	GLP-1 / amylin long acting co-agonist	Phase 1	Oral	Early 2024
Pfizer (PFE)	Danuglipron (PF-06882961)	Oral GLP-1 agonist	Phase 2	Oral, twice-daily	Discontinued
Pfizer (PFE)	Lotiglipron (PF-07081532)	Oral GLP-1 agonist	Phase 2	Oral, once daily	Discontinued
Rhythm Pharmaceuticals (RYTM)	Setmelanotide (IMCIVREE; f/k/a: CAM-4072)	Melanocortin Receptor 4 (MC4R) agonist	Approved	Oral	Label expansions; TBD
Roche (RHHBY)/ Carmot	CT-388	GLP-1/ GIP receptor agonist	Phase 1/2	SC, once weekly	1H24 data for cohorts 9,11 and 12
Roche (RHHBY) / Carmot	CT-996	GLP-1 receptor agonist	Phase 1	Oral	1H24 SAD/MAD data
Shionogi (OTC: SGIOY)	S-309309	Oral MGAT2 (monoacylglycerol acyltransferase 2) inhibitor	Phase 2	Oral	Initiate Global Phase 3 TBD
Structure Therapeutics (GPCR)	GSBR-1290	GLP-1R agonist	Phase 2a/2b	Oral	Phase 2a obesity data 2Q24; Initiate phase 2b in 2H24 (275 pts, 36 wk study)
Structure Therapeutics (GPCR)	GSBR-Next Gen	Dual GLP-1R/GIPR agonist	Discovery	Oral	TBD

Exhibit 42: Obesity Competitive Landscape
There are multiple new entrants to the obesity space

Company	Drug	MoA / Target	Development Stage	Admin	Catalyst
Terns Pharmaceuticals (TERN)	TERN-601	GLP-1R agonist	Phase 1	Oral	Topline data 2H24
Terns Pharmaceuticals (TERN)	TERN-800 Series	GIPR modulators	Discovery	Oral	Candidate nomination and initiation of IND-enabling activities expected in 2024
Tonix Pharmaceuticals (TNXP)	TNX-1900	Oxytocin	Phase 2	Intranasal	Primary completion 2026
Viking Therapeutics (VKTX)	VK2735	Dual GLP-1R/GIPR agonist	Phase 2	SC, once weekly	Venture Phase 2 Results, 1H24
Viking Therapeutics (VKTX)	Oral VK2735	Dual GLP-1R/GIPR agonist	Phase 1	Oral	Phase 1 Results in HV, 1Q24
Zealand Pharma A/S (OTC: ZLDPF)	Dapiglutide (ZP 7570)	GLP-1/GLP-2 dual agonist	Phase 2	SC, once weekly	1H24 DREAM trial results; 2H24 phase 1b results
Zealand Pharma A/S (OTC: ZLDPF)	Petrelintide	Amylin analog (long acting)	Phase 1	SC, once weekly	16 week MAD study, data expected 1H24; initiate phase 2 in 2H24
Zealand Pharma A/S (OTC: ZLDPF)	ZP 6590	GIP receptor agonist (long-acting GIP analog)	Preclinical	SC, once weekly	Advance into Phase 1
Zealand Pharma A/S (OTC: ZLDPF) + Boehringer Ingelheim	survodutide	Glucagon/ GLP-1 receptor agonist	Phase 3	SC, once weekly	3 Global registrational studies; primary completion Dec 2025 for 2/3 studies

Source: BofA Global Research, T2D: Type 2 diabetes, GLP-1: glucagon-like peptide 1, GIPR: gastric inhibitory polypeptide receptor, YY: peptide, SC: subcutaneous, IV: intravenous, IND: investigational new drug, PoC: proof of concept

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While there are many new entrants, most are in early stages of development. Below we highlight clinical results for some of the later stage assets + ones we have more conviction on (Exhibit 43). Overall, Lilly and Novo remain leaders on efficacy, but we suspect newer entrants could differentiate on 1) safety, 2) tolerability, and 3) limited titration schemes. Indeed, to unlock the true TAM for AOMs, we suspect that primary care physicians (PCPs) need to feel comfortable prescribing AOMs and to do that, we'll need to see improvements on these metrics according to our channel checks. Moreover, improvements in these metrics could also go a long way in reducing discontinuation rates, thus increasing persistence which has been an overhang with approved therapies.

Exhibit 43: Overview of clinical results for select assets in development
Lilly and Novo remain leaders with next-generation assets, but new entrants can differentiate on safety + tolerability

					% placebo-controlled weight loss			
Company	Drug	Mechanism	Phase	Dosing	4 wks	8 wks	12 wks	52 wks
Lilly	Zepbound (5mg)	GLP-1/ GIP receptor agonist	Approved	SC/QW	3%	4.50%	7%	14%
	Zepbound (15mg)				3%	4.50%	8%	19%
	retatrutide	GLP-1/ GIP/ Glucagon receptor agonist	3	SC/QW	4%	7%	11%	22.1%^
	orforglipron (45mg)	GLP-1 receptor agonist	3	Oral/QD	2.5%	5%	6.50%	
Novo	Wegovy	GLP-1 receptor agonist	Approved	SC/QW	1.50%	2%	4%	13.00%
	CagriSema (2.4mg/2.4mg)	GLP-1 agonist + amylin	3	SC/QW	3%	5%	7%	
Altimmune	pemvidutide (2.4mg)	GIP-1/ Glucagon receptor agonist	2	SC/QW	2%	4%	6%	13.6%^
Amgen	mari-tide (120mg)	GLP-1 receptor agonist/ GIP receptor antagonist	2	SC/Q4W	4%	6%	7%	
	mari-tide (420mg)				7%	12%	15%	
Boehringer Ingelheim	survodutide	GIP-1/ Glucagon receptor agonist	3	SC/QW				18.7%*
Structure	GSBR-1290 (90mg)	GLP-1 receptor agonist	1/2	Oral/QD	4.90%			
	GSBR-1290 (120mg)				~2.7%	4.74%		
Roche/ Carmot	CT-388	GLP-1/ GIP receptor agonist	1/2	SC/QW	7.80%			
Viking	VK2735	GLP-1/ GIP receptor agonist	2	SC/QW	6.00%			

Source: BofA Global Research, Company Reports, GLP-1: glucagon-like peptide 1, GIPR: gastric inhibitory polypeptide receptor, SC: subcutaneous, QD: once a day, QW: only weekly, Q4W: once every four weeks, *Week 46 results, ^Week 48 results

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Regardless of the competition, Lilly and Novo continue to invest in lead assets
Both Lilly and Novo are running a multitude of trials for lead assets, including tirzepatide, orforglipron, and retatrutide for Lilly + next-generation CagriSema for Novo.

In our view, this speaks to both Lilly and Novo's conviction in the commercial opportunity as the companies have increased R&D and SG&A spend to further bolster the assets clinical profiles.

Exhibit 44: Overview of clinical trials for tirzepatide
Lilly is running >15 clinical trials for tirzepatide

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
NCT04184622	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1	3	2539	Percent Change from Baseline in Body Weight	Apr-22
NCT05822830	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight With Weight Related Comorbidities (SURMOUNT-5)	3	700	Percent Change from Baseline in Body Weight	Nov-24
NCT06075667	Obesity	A Study of Tirzepatide (LY3298176) Once Weekly in Adolescent Participants Who Have Obesity, or Are Overweight With Weight-Related Comorbidities (SURMOUNT-ADOLESCENTS)	3	150	Percent Change from Baseline in Body Mass Index (BMI)	Feb-26
NCT06047548	Obesity	A Study of LY3298176 (Tirzepatide) For the Maintenance of Body Weight Reduction in Participants Who Have Obesity or Overweight With Weight-Related Comorbidities (SURMOUNT-MAINTAIN)	3	400	Percent Maintenance of Body Weight (BW) Reduction Achieved during the 60-Week Weight Loss Period	May-26
NCT05556512	Obesity	A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)	3	15000	Time to First Occurrence of Any Component Event of Composite (All-Cause Death, Nonfatal Myocardial Infarction (MI), Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events	Oct-27
NCT04255433	T2D	A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT)	3	13299	Time to First Occurrence of Death from Cardiovascular (CV) Causes, Myocardial Infarction (MI), or Stroke (MACE3	Oct-24
NCT05260021	T2D	A Study to Evaluate Tirzepatide (LY3298176) in Pediatric and Adolescent Participants With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin or Basal Insulin or Both (SURPASS-PEDS)	3	90	Change From Baseline in Hemoglobin A1c (HbA1c)	Nov-24
NCT06037252	T2D	A Study of Investigational Tirzepatide (LY3298176) Doses in Participants With Type 2 Diabetes and Obesity	2	350	Percent Change From Baseline in Body Weight	Dec-24
NCT04166773	NASH	A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (SYNERGY-NASH)	2	196	Percentage of Participants with Absence of NASH with no Worsening of Fibrosis on Liver Histology	Jan-24
NCT05412004	Sleep Apnea	Obstructive Sleep Apnea Master Protocol GPIF: A Study of Tirzepatide (LY3298176) in Participants With Obstructive Sleep Apnea (SURMOUNT-OSA)	3	469	Percent Change from Baseline in Apnea-Hypopnea Index (AHI)	Mar-24
NCT04847557	HFpEF	A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity (SUMMIT)	3	700	A Hierarchical Composite of All-Cause Mortality, Heart Failure Events, 6-minute Walk Test Distance (6MWD) and Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) Category	Jun-24
NCT05536804	CKD	A Study of Tirzepatide (LY3298176) in Participants With Overweight or Obesity and Chronic Kidney Disease (CKD) With or Without Type 2 Diabetes (TREASURE-CKD)	2	140	Change from Baseline in Kidney Oxygenation in Participants With or Without T2D [Time Frame: Baseline, Week 52]; Blood oxygenation-level dependent magnetic resonance imaging (BOLD MRI)	Jan-26

Source: BofA Global Research, clinicaltrials.gov, company reports

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Exhibit 45: Overview of clinical trials for orforglipron
Lilly is running >7 clinical trials for orforglipron

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
NCT06010004	T2D	A Phase 3, Long-term Safety Study of LY3502970 in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise Alone or in Combination With Oral Antihyperglycemic Medications (ACHIEVE-J)	3	399	Number of Participants with Treatment Emergent Adverse Events (TEAEs) [Time Frame: Baseline through Week 52]	Jun-25
NCT05803421	T2D	A Phase 3, Open-Label Study of Once Daily LY3502970 Compared With Insulin Glargine in Adult Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk (ACHIEVE-4)	3	2620	Time to First Occurrence of Any Major Adverse Cardiovascular Event (MACE-4) [Myocardial Infarction (MI), Stroke, Hospitalization for Unstable Angina, or Cardiovascular (CV) Death] [Time Frame: Baseline to End of the Study (Approximate Maximum 104 Weeks)]	Apr-25
NCT05931380	Obesity	A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared With	3	236	Mean Percent Change in Body Weight [Time Frame: Baseline, Week 72]	Jun-25

Exhibit 45: Overview of clinical trials for orforglipron
Lilly is running >7 clinical trials for orforglipron

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
		Placebo in Japanese Adult Participants With Obesity Disease (ATTAIN-J)				
NCT05869903	Obesity	A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared With Placebo in Adult Participants With Obesity or Overweight With Weight-Related Comorbidities (ATTAIN-1)	3	3000	Mean Percent Change from Baseline in Body Weight [Time Frame: Baseline to Week 72]	Sep-25
NCT05872620	Obesity	A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared With Placebo in Adult Participants With Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)	3	1500	Mean Percent Change from Baseline in Body Weight [Time Frame: Baseline, Week 72]	Jun-25
NCT05971940	T2D	A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once Daily Oral LY3502970 Compared With Placebo in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Diet and Exercise Alone	3	520	Change from Baseline in Hemoglobin A1c (HbA1c) [Time Frame: Baseline, Week 40]	Jan-25
NCT06045221	T2D	A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral LY3502970 Compared With Oral Semaglutide in Adult Participants With Type 2 Diabetes and Inadequate Glycemic Control With Metformin (ACHIEVE-3)	3	1576	Change from Baseline in Hemoglobin A1c (HbA1c) [Time Frame: Baseline, Week 52]	Jul-25
NCT06109311	T2D	A Study of Orforglipron (LY3502970) in Participants With Type 2 Diabetes and Inadequate Glycemic Control With Insulin Glargine, With or Without Metformin and/or SGLT-2 Inhibitor (ACHIEVE-5)	3	520	Change from Baseline in Hemoglobin A1c (HbA1c) Compared to Placebo	Apr-25

Source: BofA Global Research, clinicaltrials.gov, company reports

BofA GLOBAL RESEARCH

Exhibit 46: Overview of clinical trials for retatrutide
Lilly is running 5 clinical trials for retatrutide

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
NCT05882045	Obesity	A Randomized, Double-Blind, Phase 3 Study to Investigate the Efficacy and Safety of LY3437943 Once Weekly Compared to Placebo in Participants With Severe Obesity and Established Cardiovascular Disease (TRIUMPH-3)	3	1800	Percent Change from Baseline in Body Weight [Time Frame: Baseline, Week 80]	Jan-26
NCT05931367	Obesity	A Phase 3 Study to Investigate the Efficacy and Safety of LY3437943 Once Weekly in Participants Who Have Obesity or Overweight and Osteoarthritis of the Knee: A Randomized, Double-Blind, Placebo-Controlled Trial (TRIUMP-4)	3	405	Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score [Time Frame: Baseline, Week 68]	Feb-26
NCT05929066	Obesity	A Master Protocol to Investigate the Efficacy and Safety of LY3437943 Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (TRIUMPH-1)	3	2100	Percent Change From Baseline in Body Weight [Time Frame: Baseline, Week 80]	Apr-26
NCT05929079	Obesity	A Master Protocol to Investigate the Efficacy and Safety of LY3437943 Once Weekly in Participants With Type 2 Diabetes Mellitus Who Have Obesity or Overweight: A Randomized Double-Blind, Placebo-Controlled Trial (TRIUMPH-2)	3	1000	Percent Change from Baseline in Body Weight [Time Frame: Baseline, Week 80]	May-26
NCT05936151	Chronic Kidney Disease	A Phase 2b, Double-Blind Study to Investigate the Effect of LY3437943 on Renal Function in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes	2	120	Change from Baseline in Glomerular Filtration Rate (GFR) [Time Frame: Baseline, Week 24]	Nov-25

Source: BofA Global Research, clinicaltrials.gov, company reports

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Exhibit 47: Overview of clinical trials for CagriSema
Novo is running >7 trials for CagriSema

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
NCT05567796	Obesity	A Research Study to See How Well CagriSema Helps People With Excess Body Weight Lose Weight (REDEFINE 1)	3	3400	CagriSema 2.4 mg/2.4 mg versus placebo: Relative change in body weight and CagriSema 2.4 mg/2.4 mg versus placebo: Achievement of greater than or equal to (>=) 5% weight reduction [Timeframe: From baseline (week 0) to end of treatment (week 68)]	Oct-24

Exhibit 47: Overview of clinical trials for CagriSema
Novo is running >7 trials for CagriSema

Study	Indication	Title	Phase	Patients	Primary Outcome	Primary Completion
NCT05394519	Obesity / T2D	A Research Study to See How Well CagriSema Helps People With Type 2 Diabetes and Excess Body Weight Lose Weight (REDEFINE 2)	3	1200	Relative change in body weight (Measured in %) and Achievement of greater than or equal to 5% weight reduction (Count of participant) [Timeframe: From baseline (week 0) to end of treatment (week 68)]	Dec-24
NCT05669755	CVD	A Research Study to See the Effects of CagriSema in People Living With Diseases in the Heart and Blood Vessels (REDEFINE 3)	3	7000	Time to first occurrence of major adverse cardiovascular event (MACE), a composite endpoint consisting of: cardiovascular (CV) death, non-fatal myocardial infarction, non-fatal stroke [Timeframe: Baseline (week 0) to end of study (up to 242 weeks or more)]	Sep-27
NCT05996848	Obesity	A Research Study to See How Well CagriSema Helps People in China With Excess Body Weight Lose Weight (REDEFINE 6)	3	300	CagriSema 2.4 mg/2.4 mg versus placebo: Relative change in body weight (Measured in percentage (%)) and CagriSema 2.4 mg/2.4 mg versus placebo: Number of participants who achieve (yes/no): Body weight reduction greater than or equal to 5% (Measured as count of participants) [Timeframe: Baseline (week 0) to end of treatment (week 44)]	Feb-25
NCT05813925	Obesity	A Research Study to See How Well CagriSema Helps People in East Asia With Excess Body Weight Lose Weight	3	330	Relative Change in Body Weight [Timeframe: From baseline (week 0) to end of treatment (week 68)]	Jan-25
NCT06065540	T2D	A Research Study to See How Well CagriSema Compared to Semaglutide, Cagrilintide and Placebo Lowers Blood Sugar and Body Weight in People With Type 2 Diabetes Treated With Metformin With or Without an SGLT2 Inhibitor (REIMAGINE 2)	3	2700	CagriSema versus semaglutide (2.4 mg/2.4 mg versus 2.4 mg and 1.0 mg/1.0 mg versus 1.0 mg): Change in glycated haemoglobin (HbA1c) Measured in percentage points [Timeframe: Baseline (week 0) to end of treatment (week 68)]	Nov-25
NCT06131437	Obesity	Efficacy and Safety of Cagrilintide 2.4 mg s.c. in Combination With Semaglutide 2.4 mg s.c. (CagriSema s.c. 2.4 mg/2.4 mg) Once-weekly Compared to Tirzepatide 15 mg s.c. Once-weekly in Participants With Obesity	3	800	Relative change in body weight [Time Frame: From baseline (week 0) to end of treatment (week 72)]	Aug-25
NCT06131372	CKD/ T2D	Efficacy and Safety of Co-administered Cagrilintide and Semaglutide (CagriSema 2.4 mg/2.4 mg) Once Weekly Versus Semaglutide 2.4 mg, Cagrilintide 2.4 mg and Placebo in People With Chronic Kidney Disease and Type 2 Diabetes Living With Overweight or Obesity	2	618	Change in urinary albumin-to-creatinine ratio (UACR) [Time Frame: From baseline (week 0) to end of treatment (week 26)]	Oct-25

Source: BofA Global Research, clinicaltrials.gov, company reports

BofA GLOBAL RESEARCH

2) Pain: A focus on next-generation non-opioid alternatives

Given the opioid epidemic, there has been a focus on new mechanisms to reduce pain, but so far, there hasn't been much progress, just terminated programs. Indeed, Pfizer, Abbott, Amgen, Astellas, Biogen, Xenon, Roche, and Vertex have all terminated programs due to a combination of 1) lack of efficacy and 2) unfavorable tolerability + PK/PD (pharmacokinetic/pharmacodynamic) profiles. That said, given Vertex's recent progress with NaV1.8 inhibitor, VX-548, in acute and neuropathic pain, we've seen a reinvigoration of the space which we expect to continue into 2024 as we await Vertex's three phase 3 results in acute pain (expected early 2024). Indeed, the unmet need in both acute and neuropathic pain is high according to our KOLs, particularly in neuropathic pain (see below), where Lyrica or pregabalin, is used as the gold standard.

KOL quotes on the unmet need in neuropathic pain

"Lyrica, which we all consider, and especially when it came out, we considered it to be a groundbreaking drug. And the only reason it's not groundbreaking now is because it's been almost 20 years. That's the only reason, right? But if we lost access to Lyrica, which we have in many ways because of insurance, people suffer. We've had patients who really are not doing very well because they were forced to switch to a generic."

"So, in those patients that were forced to switch off [Lyrica], it just shows you how that if Lyrica is still a pretty awesome drug, but those patients who are forced to switch off Lyrica or didn't tolerate Lyrica, or those patients who Lyrica wasn't effective enough, or whatever

the case may be. If we can offer them a complementary alternative, we are going to hop all over it all day long."

Where does Vertex stand?

Vertex has a broad pipeline to treat pain, including three NaV1.8 inhibitors in clinical development (lead VX-548 (oral), VX-993 (oral), and VX-973(oral/ I.V.)) and early stage NaV1.8 and NaV1.7 inhibitors in preclinical development (see Exhibit 48). VX-548 is Vertex's lead asset, where we expect three phase 3 results in acute pain in early 2024, which if positive, could support a broad, moderate-to-severe acute pain and allow for prescribing + use in multiple different care settings. In neuropathic pain, Vertex just completed a phase 2 trial in diabetic peripheral neuropathy (DPN) which looked favorable to us as VX-548 was numerically better than the other active arm, Lyrica (see our thoughts on VX-548's results here). The next steps in DPN are to complete a phase 2 meeting with FDA to talk through the specifics on design of the pivotal phase 3, including the patient population and the primary + secondary endpoints as Vertex is targeting a broad peripheral neuropathic pain (PNP) label. Notably, Vertex has initiated a phase 2 trial for VX-548 in Lumbosacral radiculopathy (LSR) and is currently enrolling patients, with the primary completion April 2024.

Exhibit 48: Vertex's pain pipeline
We highlight Vertex's pain pipeline, with acute focus on lead asset VX-548

Asset	Indication	Modality	Research	Phase 1	Phase 2	Phase 3	Approved
VX-548	Acute pain	Oral					
VX-548	Diabetic peripheral neuropathy	Oral					
VX-548	Lumbosacral radiculopathy	Oral					
VX-993	-	Oral					
VX-973	-	Oral					
VX-993	-	IV					
Other NaV1.8 inhibitors	-	Oral/ IV					
NaV1.7 inhibitors	-	-					

Source: BofA Global Research, Company Reports

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There has been some skepticism on VX-548 in acute pain following the full results in The New England Journal of Medicine and the accompanying editorial that questioned the magnitude of the clinical benefit and the lack of a dose response. However, following the phase 2 results in DPN, which added to the body of evidence for efficacy, safety, and tolerability for VX-548, we'd say investors are more positive on the likelihood of a positive readout for the acute pain trials in early 2024. Indeed, if VX-548 is able to recapitulate the results from the phase 2 trial in the pivotal phase 3, we'd say the results would be a home run based on our channel checks. However, there are a multitude of commercial hurdles, particularly for acute pain, see below.

KOL quotes on Vertex's NaV1.8 asset, VX-548

"Vertex to me is like the Buffalo Bills of drug companies or neuropathic pain companies. They've lost more Super Bowls than anyone else."

"So, we're crossing our fingers especially in an environment where we continue to be opioid phobic. The FDA actually has a little more pressure to approve medications that are non-opioids. So, we'll see. But I definitely remain cautiously optimistic. If someone forced me to make a prediction, I would probably say that in some iteration it'll get approved. If I if I had to make a wild guess and it's anybody's guess at this point, it's anybody's guess."

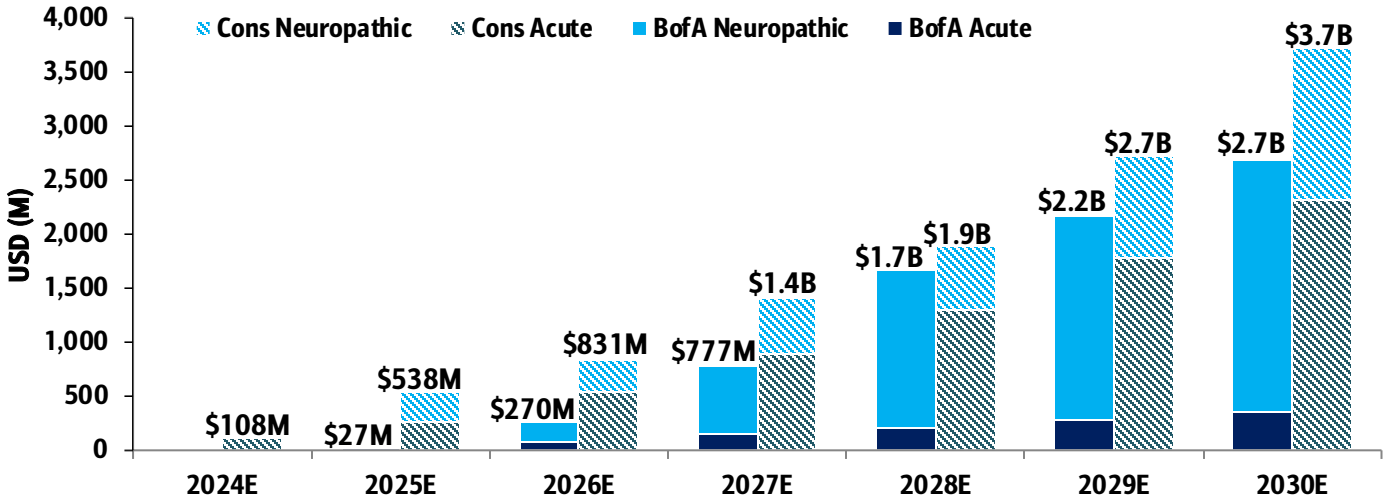
"But the question really becomes if Vertex can show that their product is comparable to Lyrica, can they get approval with that? Do they need to necessarily be more efficacious than Lyrica? I don't think so. I mean, Lyrica is considered a blockbuster drug. And you need to be twice as good as a blockbuster drug. I mean, I don't think so. Especially in an environment where we're desperately seeking out alternatives to opioids. So I don't think so. I think if you show efficacy that's consistent with Lyrica, I, I think it should be good enough for approval."

"Nobody is on monotherapy. Or at least 95% plus of people are not on monotherapy. We're always using polypharmacy to help people, or at least polytherapy to help people. So, could you potentially use Lyrica along with vertex 548? In theory, sure. I mean, unless there's something that both drug companies tell us that we should not combine them or whatever."

What do we see as the commercial opportunity? What are the hurdles?

Based on our channel checks, we continue to suspect that the commercial opportunity for VX-548 is larger in neuropathic pain versus acute pain. That said, while all indicators point to a large market for neuropathic pain, it's still challenging to tease out the potential peak revenue/ scripts using analogues such as Lyrica, as patients tend to cycle on and off therapies due to lack of insurance coverage/ entrance of generics and side effects leading to discontinuations. Nevertheless, we forecast revenue of >$2.5B for VX-548 in acute + neuropathic pain in 2030 as compared to >$3.5B for consensus (Exhibit 49). Ultimately, we suspect the Street hasn't taken into consideration the commercial hurdles in acute pain given the business case at hospitals, where 1) generic opioids are entrenched and "cheap", 2) the goal is to have patients leave the hospital following surgery as quickly as possible to reduce costs, but the onset of action for VX-548 is slower than opioids, and 3) building awareness for new drugs is challenging as hospitals are chronically understaffed + typically prefer to stick to what they know (see below for quotes from our KOLs + Vertex). Indeed, we suspect the launch in acute pain will be slower and less robust than in neuropathic pain given the above constraints, especially as in neuropathic pain there is less bureaucracy to treatment—e.g., patients are typically not treated in hospital settings. Moreover, in neuropathic pain while we initially expect VX-548 to be 3rd line after over-the-counter drugs (e.g., Non-steroidal anti-inflammatory drugs (NSAIDs)) and gabapentin / Lyrica because of "cost", we expect it to move to 2nd line after a few years on the market based on our KOL discussions, further bolstering our long-term forecasts.

Exhibit 49: The commercial opportunity in pain is robust
We forecast >$2.5B in sales by 2030 for VX-548 in acute and neuropathic pain vs. >$3.5B for consensus



Source: BofA Global Research, VisibleAlpha

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KOL quotes on the commercial opportunity in pain

"But with diabetic peripheral neuropathy, it's a pretty well-understood disease. I think anyone who treats it understands. I mean, we only have a limited toolbox and they all understand that. And I think everyone is like, look, we need we need more tools in our toolbox. And the faster you can give them to us, the better. So, there's not and there's no hospital involved and there's no surgeon involved and no hospital pharmacy and this and that. The only people involved here are going to be the treating physician, the patient and whoever their insurance company is. Insurance companies typically give push back no

matter what because they don't want to pay. They don't want to pay for more expensive products."

"It's a business issue. It has nothing to do with quality. And it's an awful, awful thing to say. It's the truth. But it's an awful thing to say. And that's why I don't think it's going to it's going to be a much harder push in the acute pain side, especially in the post-surgical side, than it is with the chronic pain side."

"There have been a lot of acute pain drugs that are quite amazing, that have come and gone. When I say gone, I'm talking about literally off the market because they couldn't get the hospitals to sign on. They couldn't get the insurance companies to sign on. You couldn't get the physicians to sign on. And we're talking about products that actually would knock the socks off of Vertex's 548"

"I just don't see it happening on the acute pain side. I see it happening on the chronic pain side. I just don't see it happening on the acute pain side."

"I don't know if it'll be first line, but it would be eventually it would be the same line as Lyrica, which is not first. It might be second. Maybe third, but not first."

Quotes from Vertex on VX-548

"There are approximately 10 million patients treated for PNP each year in the U.S. representing another multibillion dollar market today in the U.S. despite the fact that here to essentially all prescriptions are generics. Nearly 20% of these patients have diabetic peripheral neuropathy or DPN and over 40% have lumbosacral radiculopathy or LSR."

"Our overarching goal in the PNP segment is to gain a broad neuropathic pain label, and we see the opportunity to do so with clinical studies in DPN and LSR, which, when combined, represent approximately two-thirds of the PNP patient population in the U.S."

"So obviously, there will be pricing and contracting issues to work through, but we certainly see a path of being able to commercialize 548 in both settings. And as Reshma said in her prepared remarks, both of them have significant unmet need, both of them have very poor treatment options available today, and we are more confident than ever with these data in hand that VX-4548 has the potential to be a multibillion dollar product if it's successful in its studies and gets regulatory approval."

"On payers, I would say they are well aware of the unmet need in the treatment of neuropathic pain. They're well aware that the existing agents have variable efficacy, that there are high rates of discontinuations and switches and that sort of thing, as I've described earlier. So, they are very well aware of that. They're very interested in new treatment options coming forward, which have a superior benefit risk profile.

As you referenced, everything else that's currently used is generic. And so they are going to be looking for something that has a strong benefit risk profile. And based on the data we've got with 548 in Phase 2, we're super excited to take it forward into Phase 3, where we're going to be able to more fully elucidate the full profile of 548. And we're excited to see what that shows and then take that to payers."

"Acute pain, as we've said, affects about 80 million Americans per year. Neuropathic pain, chronic neuropathic pain affects about 10 million patients a year. But by definition, those patients are in chronic pain. Those people are in pain every single day of their lives and therefore looking for relief every day of their lives.

The markets in terms of revenue are approximately the same size today, despite both of them being 90% plus genericized. The chronic neuropathic pain market is also around about 4 billion in revenue today."

Potential for Congressional Acts

There's been a multitude of legislative proposals to limit opioid prescriptions and provide payments for non-opioid alternatives, which both Vertex and investors have

pointed to as potential avenues to increase penetration of VX-548 given the commercial hurdles (see above). Indeed, the No Pain Act was passed as part of year-end legislation last year (Dec. 2022) and includes: a temporary separate payment (2025-2027) for certain non-opioid treatments under the Medicare prospective payment system for hospital outpatient department services and the payment system for ambulatory surgical center services and applies to pain management treatments that can replace or reduce opioid consumption, as shown through clinical trials or data. That said, the Centers for Medicare & Medicaid Services (CMS) has yet to implement these provisions to provide the separate payment – even as advocates have called on CMS to accelerate the implementation to 2024. CMS has stated that it can only implement the provisions in 2025 – not 2024 – and the additional payments are slated to end on December 31, 2027, which highlights the challenges of this types of legislation, in our view. Moreover, while the SUPPORT act was recently reauthorized by the house, which also incentivizes non-opioid options through an Action Plan and New Pain codes, the House still needs to find agreement with the Senate on the Bill, with the hope that it can be included in a continuing resolution (CR), or government funding Bill in January as Government funding expires on January 19th, so that's the new target date. Other Federal Agencies have also joined the discussion, with the National Institutes of Health (NIH) instituting the NIH HEAL Initiative and the Pain Management Collaboratory (PMC) to expand access to non-opioid therapies for pain management. Overall, we'd argue both Bills highlight that while legislation can be passed to increase access + funding for non-opioid alternatives, but there are a multitude of hurdles before they can be implemented. Indeed, our KOLs remain less optimistic about the potential for legislation to broaden access for non-opioid pain alternatives than Vertex (see below), which is one of the reasons why we model a slow launch for both acute and neuropathic pain.

KOL quotes on the potential for Congressional Acts

"I'm unfortunately old enough to know that that's a pipe dream [legislation to open up access for non-opioid pain medications]. Young enough to still be naive enough to think that we all make a difference in this world, but old enough to know that that's something out of a marvel movie. maybe some superhero movie. It's true. Look, it just comes back to one solitary thing. Who's got the bigger lobby?"

"Even the lawmakers, if they take pharma money, it's considered evil. But if they take insurance company money, it's okay. So that's why that law will never get passed. Right. That's why it's not going to get past."

3) Antibody-Drug Conjugates: Revolutionizing the Cancer Treatment Paradigm

ADC technology has gained significant interest in recent years, owing to commercial success (7 approved for 10 indications) and ongoing Biopharma BD activity. Indeed, 2023 had been a very busy year for ADCs, with multiple acquisitions/collaborations (e.g., Pfizer/ Seagen, AbbVie/ Immunogen, Merck/ Daiichi, and Bristol/SystImmune) and important data readouts (e.g., Padcev's EV-302, Elahere's MIRASOL, Dato-DXd's TROPION-Lung01/Breast01, and Trodelvy's Evoke-02). We expect interests in ADCs to remain elevated in 2024, especially in hard-to-treat cancers where IO-based regimen hasn't found much success as well as IO/ ADC combo regimens in front-line setting, where we expect to see incremental data updates and continuous debate on the which ADCs will likely reign over the crowded market, potentially becoming the next PD-1s.

Indeed, in 2023 we witnessed many discussions among KOLs and the investor community, focusing on the impact of ADCs in changing treatment paradigms presented at AACR, ASCO, and ESMO, including both incremental and ground-breaking results from late-stage/commercial ADCs such as Enhertu, Trodelvy, Padcev, Dato-DxD. Importantly, investors continue to look for the next ADC agents with the potential to offer a greater efficacy/safety profile, and there's a sense of excitement about emerging ADC targets, including B6A, c-MET, Claudin 18.2, and B7H3.

Exhibit 50: 2023 ADC M&A and licensing deals
Pfizer/Seagen and AbbVie/ImmunoGen were of the largest HC M&A deals in 2023 with >$50B in combined value

Date	Acquirer	Acquiree/ Partner	Deal Type	Deal size	Key ADC Assets	Dev Stage
12/22/2023	J&J	LegoChem Bio	Licensing	Up to $1.7B ($100M upfront)	LCB84 (TROP2) in solid tumors	Clinical
12/20/2023	GSK	Hannosh	Licensing	$185M upfront + $1.5B milestone + royalties	HS-20093 (B7-H3) for lung cancer, sarcoma, H&N cancers	Clinical
12/11/2023	Bristol Myers	SystImmune	Licensing	Uo to $8.4B ($800M upfront)	BL-B01D1 (EGFRxHER3) for NSCLC	Clinical
12/7/2023	Innovent	Synaffix	Licensing	Not disclosed	Expanded collaboration	Preclinical
11/30/2023	AbbVie	ImmunoGen	Acquisition	$10.1B	Elahere (FRα) for ovarian cancer	Commercial
11/6/2023	Bristol Myers	Orum	Program Acquisition	$100M upfront + $80M milestone	ORM-6151 (CD33 GSPT1 degrader) for AML and myelodysplastic syndromes	Clinical
10/20/2023	GSK	Hannosh	Licensing	$85M upfront + $1.5B milestones + royalties	HS-20089 (B7-H4) for endometrial / ovarian cancers	Clinical
10/19/2023	Merck	Daiichi Sankyo	Licensing	Up to $22B ($4B upfront)	HER3-DXd (HER3) for EGFR lung /breast cancers , I-DXd (B7H3) for SCLC, R-DXd (CDH6) for ovarian cancer	Clinical
10/19/2023	Endeavor Bio	Humingbird Bio	Licensing	Up to $430M + royalties	HMBD-501 (HER3)	Preclinical
10/18/2023	Eli Lilly	Mablink Bio	Acquisition	Not disclosed	linker technology	Preclinical
10/16/2023	SOTIO	Synaffix	Licensing	Up to $740M + royalties	antibody conjugation technology	Preclinical
10/12/2023	BioNTech	MediLink	Licensing	$70M upfront + $1B milestone	YL202 (HER3) for EGFR lung / HER2- breast cancer	Clinical
9/13/2023	ABL Bio	Synaffix	Licensing	Not disclosed	antibody conjugation technology	Preclinical
7/10/2023	Beigene	DualityBio	Licensing	Up to $1.3B + royalties	Not disclosed	Preclinical
6/1/2023	Lonza	Synaffix	Acquisition	€100 cash + €60M milestone	antibody conjugation technology	Preclinical
5/12/2023	AstraZeneca	LabNova	Licensing	Up to $545M + royalties	LM-305 (GPRC5D)	Preclinical
4/13/2023	Pyramid Bio	GeneQuantum	Licensing	$20M upfront + $1B milestone	GQ1010 (TROP2)	Preclinical
4/10/2023	Bristol Myers	Tubulis	Licensing	$23M + $1B milestone + royalties	P5 conugation platform	Preclinical
4/3/2023	BioNTech	DualityBio	Licensing	$170M upfront + $1.5B milestone + royalties	DB-1303 (HER2) for solid tumors, DB-1311 (B7-H3) for solid tumors	Clinical
3/14/2023	MacroGenics	Synaffix	Licensing	Upo to $2.2B + royalties	antibody conjugation technology	Preclinical
3/13/2023	Pfizer	Seagen	Acquisition	$43B	Padcev (Nectin-4) for urothelial carcinoma, Adcetris (CD30) for cHL, Tivdak (TF) for cervical cancer	Commercial
1/5/2023	Amgen	Synaffix	Licensing	Up to $2B + royalties	antibody conjugation technology	Preclinical
1/4/2023	Hummingbird Bio	Synaffix	Licensing	Uo to $150M + royalties	antibody conjugation technology	Preclinical

Source: BofA Research, Company Data

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What is ADC and how did it become a topic du jour? While the development of ADC or antibody-drug-conjugate has been around for many decades, it wasn't until 2000 when the first ADC, Pfizer's Mylotarg, was approved for the treatment of AML. However, it would take another 11 years before the second ADC, Seagen's Adcetris, receive the FDA approval. That said, interests in ADCs really only took off over the past few years owning to the approval and commercial success of Astra/Daiichi's Enhertu, Seagen's Padcev, and Gilead's Trodelvy in cancers where immune-oncology (IO) has fell short. Indeed, the overwhelming success of IO therapy in becoming the standard of care (replacing chemotherapy) have marked a therapeutic renaissance in the treatment of solid tumors. However, most patients still relapse despite the initial response, with chemotherapies as the only salvage treatment options, which come with less than favorable efficacy/tolerability profile. Indeed, in theory ADC should be able provide the benefit of chemotherapy without the safety/tolerability baggage; however, in practice it's been difficult to develop an ADC with attractive efficacy/safety profile.

ADCs development is challenging

ADCs are highly complex and difficult to develop, given factors such as the choice of target/indication, antibody, payload, and linker, all of which need to work in harmony. For example, tumor antigen expression limits the amount of ADC payload that can be delivered to the inside of cells (via target binding), and drug-to-antibody ratio (DAR) can impact PK/PD profile. As such, optimizing ADCs is difficult, and their efficacy/safety profiles are hard to predict based on preclinical models. Furthermore, while the efficacy of ADCs depends on target binding, there's no consistency in the utility of these biomarkers (e.g., TROP2 expression is not a patient selection criterion while HER2 mutation status is). Importantly, KOLs believe that ADCs will become the standard of care in many cancers and in earlier disease settings (neoadjuvant). Indeed, the field continues to evolve with new agents using novel linkers and cytotoxic, as well as combination strategies with other anticancer agents, such as IO therapy.

Overcoming resistance

A key issue in cancer treatment lies in the rise of tumor resistance after cancer therapy, which causes patients to relapse and move to another therapy. ADCs could be effective agents in the refractory setting because 1) ADCs have demonstrated anti-tumor activity in patients with diverse mechanisms of resistance and genomic alterations (e.g., HER3 and TROP2, respectively) and 2) patients with prior ADCs can still respond to different ADCs targeting the same molecules. For example, HER3 ADC could be used in EGFR-resistant patients post-Tagrisso treatment because HER3 is upregulated in EGFR inhibitor-treated patients, resulting in increased internalization of HER3 ADC in the cell and release of cytotoxic payload.

ADC toxicity and safety concerns

Despite ADC's role in changing the cancer treatment paradigms, they come with unique set of toxicity profiles that need to be managed carefully. At a high level, the structure of the ADCs and their components (antibody specificity, linker characteristics, and nature of the chemo payload) are the main determinants of their efficacy/toxicity profiles. Indeed, the determinants of toxicities are due to 1) system drug release before reaching the target (toxicity according to systemic effect of the chemo payload), 2) expression of the target antigen by normal tissue, 3) uptake of ADCs and conjugates clearance, and 4) bystander effect. As such, changing one component can dramatically alter an ADC's toxicity profile (e.g., GI side effects vs. ILD/pneumonitis) or its efficacy/target indication (HER2+ vs. HER2- breast cancer). Overall, while there's no one-size fit all approach given the unique toxicity profile associated with each ADC, the experts believe that there'll be a learning curve for prescribers but expect the overall risks to come down in the real-world setting.

Who are the major ADC players and what's the competitive landscape? The competitive landscape of ADC has evolved rapidly over the past year given the number of M&A and licensing deals, as well as key data readouts. Indeed, we believe the 2023 marks the dawn of an ADC era with AstraZeneca, Merck, and Pfizer as the major ADC players ("Big Three") going forward, each armed with a suite of ADCs targeting across various cancer indications and stage of diseases. That said, the field is constant evolving and competition in oncology is fierce with other smaller players also looking to capture share. In our view, while Gilead only has one late-stage/commercial ADC (Trodelvy) in the portfolio, Trodelvy's attractive efficacy/safety profile for indications such as lung and breast cancer mean it can still achieve multi-billion blockbuster peak sales potential.

2024 a catalyst rich year ADCs

Key events include: **1)** Gilead's Trodelvy Evoke-01 in 2/3L NSCLC in 1H24, **2)** Astra's Dato-DXd filing/approval for 2/3L NSCLC in 2024, **3)** Merck's HER3-DXd potential approval in 2/3L EGFR NSCLC by June 24 and confirmatory trial readout (HERTHENA-Lung02) by, **4)** Dato-DXd US filing and potential launch in 2/3L HR+/HER2- breast cancer, **5)** Dato-DXd data in 1L TNBC (TROPION-Breast02) by YE24, and **6)** Trodelvy confirmatory results in 2L UC in 4Q24 and phase 2 data in 1L UC in 2H24.

Exhibit 51: Major ADC players
Lung and breast cancer are highly competitive given their sizable commercial opportunities

Company	Drug	Target	NSCLC	SCLC	Breast	CRC	GEA/ GI	Ovarian	UC	Others
AbbVie	Elahere	FRa						Dec 2022		
	IMGN-151	FRa								
	Pivekimab Sunrine	CD123								BPDCN, AML
	IMGC936	ADAM9								Solid tumors
	Teliso-V	cMET	Filing in Fall 2024							
	ABBV-400	cMET					GEA			
Merck/Daiichi	HER3-DXd	HER3	PDUFA 6/26/24							
	I-DXd	B7H3								
	R-DXd	CDH6								
Merck/Kelun	MK-2870	TROP2	NSCLC initiated; EGFR data in 2025		TNBC					
	MK-1200	CLDN18.2					GI tumors			
AstraZeneca/ Daiichi	Enhertu	HER2	Aug 2022		Dec 2019		Jan 2021			PanTumor filing
	Dato-DXd	TROP2	1L and 2/3L NSCLC		HR+/HER2- 2/3L BC, neoadj/ 1L TNBC					
AstraZeneca	AZD5335	FRa								
	AZD8205	B7H4								BTC, endometrial
	AZD9592	EGFR/cMET								HNSCC
	AZD0901	CLDN18.2					Gastric, GEJ, Pancreatic			
	LM-305	GPRC5D								MM
Gilead	Trodelvy	TROP2	1L and 2/3L NSCLC		Apr 2020				Apr 2021	H&N, endometrial
Pfizer	Padcev	Nectin-4							Dec 2019	
	Tivdak	TF								Cervical (Sept 2021)
	Adcetris	CD30								DLBCL (Aug 2011)
	SGN-B6A	ITB6	1L/2L NSCLC							
	DV	HER2			HER2 BC 2L				HER2 UC	

Phase 1
Phase 2
Phase 3
Approved
Regulatory

Source: BofA Research

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Exhibit 52: Key ADC clinical trials

Key trials that could change the cancer treatment paradigm over the next few years. Some trials are still being planned and no info available at this time

NSCLC	Drug Arm	Target	Indication	Trial Name	Stage	Status
AstraZeneca/Daiichi	Dato-DXd	TROP2	NSCLC 2L/3L	TROPION-Lung01	Phase 3	US filing by 1Q24
AstraZeneca/Daiichi	Dato-DXd + Keytruda/chemo	TROP2	NSCLC 1L PD-L1 <50%	TROPION-Lung07	Phase 3	Prim compl Aug 2027
AstraZeneca/Daiichi	Dato-DXd + Keytruda	TROP2	NSCLC 1L PD-L1 >50%	TROPION-Lung08	Phase 3	Prim compl Jun 2026
AstraZeneca/Daiichi	Dato-DXd + Imfinzi/chemo	TROP2	NSCLC 1L	AVANZAR	Phase 3	Prim compl May 2027
Merck/ Kelun	MK-2870 + Keytruda	TROP2	NSCLC 1L PD-L1 >50%	MK-2870-007	Phase 3	Prim compl Jan 2028
Gilead	Trodelvy	TROP2	NSCLC 2L/3L	EVOKE-01	Phase 3	Data in 1H24
Gilead	Trodelvy + Keytruda	TROP2	NSCLC 1L	EVOKE-02	Phase 2	Data at WCLC23
Gilead	Trodelvy + Keytruda	TROP2	NSCLC 1L PD-L1 >50%	EVOKE-03	Phase 3	Prim compl Jan 2027
Pfizer	SGN-B6A	ITB6	NSCLC 2L/3L	NCT06012435	Phase 3	Prim compl Nmov 2026
AbbVie	Teliso-V	cMET	cMET NSCLC	LUMINOSITY	Phase 2	Full data at ASCO 2024; AA filing Fall 2024
NSCLC - EGFR						
Merck/ Daiichi	HER3-DXd	HER3	EGFR NSCLC 2/3L	HERTHENA-Lung01	Regulatory Review	PDUFA 6/26/2024
Merck/ Daiichi	HER3-DXd	HER3	EGFR NSCLC 2/3L	HERTHENA-Lung02	Confirmatory trial	Prim compl Aug 2024
Merck/ Kelun	MK-2870	TROP2	EGFR NSCLC 2L	China Phase 3	Phase 3	Prim compl May 2025
Merck/ Kelun	MK-2870	TROP2	EGFR NSCLC 2/3L	Global Phase 3	Phase 3	Prim compl May 2027
NSCLC - HER2						
AstraZeneca/Daiichi	Enhertu	HER2	HER2 NSCLC 1L	DESTINY-Lung04	Phase 3	Prim compl: Jan 2025
Merck/ Daiichi	I-DXd	B7-H3	r/r ES-SCLC	IDeate-1	Phase 2	trial ongoing; ph3 start in FY2024
AstraZeneca/Daiichi	Enhertu	HER2	Adjuvant BC	DESTINY-Breast05	Phase 3	Prim comp Dec 2025
AstraZeneca/Daiichi	Enhertu	HER2	HER2-low BC 2L	DESTINY-Breast06	Phase 3	Data in 1H24
AstraZeneca/Daiichi	Enhertu combo	HER2	HR+/HER2- BC 2L/3L	DESTINY-Breast07	Phase 2	Prim comp Jan 2025
Breast - HER2+/HER2-						
AstraZeneca/Daiichi	Dato-DXd	TROP2	HR+/HER2- BC 2L/3L	TROPION-Breast01	Phase 3	US filing by 1Q24
Gilead	Trodelvy	TROP2	HR+/HER2- BC 3L+	ASCENT-07	Phase 3	Prim compl Sept 2025
Breast - TNBC						
AstraZeneca/Daiichi	Dato-DXd	TROP2	PD-L1- 1L TNBC	TROPION-Breast02	Phase 3	Data in 2H24
AstraZeneca/Daiichi	Dato-DXd +/- Imfinzi	TROP2	Adjuvant TNBC	TROPION-Breast03	Phase 3	Prim compl Sept 2027
AstraZeneca/Daiichi	Dato-DXd + Imfinzi	TROP2	Neoadjuvant TNBC	TROPION-Breast04	Phase 3	Prim compl Mar 2028
AstraZeneca/Daiichi	Dato-DXd + Imfinzi	TROP2	PD-L1+ TNBC 1L	TROPION-Breast05	Phase 3	Prim compl Sept 2026
Merck/ Kelun	MK-2870	TROP2	TNBC 2L	China Phase 3	Phase 3	Priority review under CDE
Gilead	Trodelvy	TROP2	PD-L1- 1L TNBC	ASCENT-03	Phase 3	Prim compl May 2027
Gilead	Trodelvy + Keytruda	TROP2	PD-L1+ 1L TNBC	ASCENT-04	Phase 3	Prim compl Feb 2027
Gilead	Trodelvy + Keytruda	TROP2	Adjuvant TNBC	ASCENT-05	Phase 3	Prim compl Jun 2027
Ovarian						
Merck/ Daiichi	R-DXd	CDH6	Ovarian cancer	Phase 1	Phase 1	Data at ESMO 2023; Ph2/3 being planned
AbbVie (Immunogen)	Elahere + Avastin	FRa	PSOC FRa high maintenance	GLORIOSA	Phase 3	Prim compl Mar 2027
AbbVie (Immunogen)	Elahere	FRa	3L+ PSOC	PICCOLO	Phase 2	Prim compl Dec 2023
AbbVie (Immunogen)	Elahere + carboplatin	FRa	2L PSOC FRa+	Trial 420	Phase 2	Prim compl Jun 2024
CRC						
AstraZeneca/Daiichi	Enhertu	HER2	HER2 mCRC	DESTINY-CRC02	Phase 2	Data at ASCO 2023
Bladder						
Gilead	Trodelvy	TROP2	2L UC	TROPiCs-04	Confirmatory trial	Prim compl Aug 2024
Gilead	Trodelvy combo	TROP2	1L UC	TROPHY U-01	Phase 2	Prim compl July 2024
Pfizer	Padcev + Keytruda	Nectin-4	1L UC	EV-302	Regulatory Review	PDUFA May 9, 2024
Pfizer	Padcev + Keytruda	Nectin-4	MIBC cis-ineligible	EV-303	Phase 3	Prim compl May 2027
Pfizer	Padcev + Keytruda	Nectin-4	MIBC cis-eligible	EV-304	Phase 3	Prim compl Dec 2026
Pfizer	DV + Keytruda	HER2	HER2+ 1L UC	NCT05911295	Phase 3	Prim compl Jun 2026
Pan-tumor						
AstraZeneca/Daiichi	Enhertu	HER2	HER2 solid tumors	DESTINY-PanTumor02	Phase 2	Data at ESMO 2023; US filing by 1Q24 as a tumor agnostic therapy
Merck/ Kelun	MK-2870	TROP2	Solid tumors	China Phase 2	Phase 2	Data in 2024
Gilead	Trodelvy	TROP2	H&N, SCLC, endometrial	TROPiCS-03	Phase 2	Data at ESMO23; Prim compl Jun 2024

Source: BofA Research, clinicaltrials.gov, Company data

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5) Emerging Markets in I&I: Lupus, Alopecia, and Vitiligo

Beyond IBD, which remains one of the higher growth markets in I&I for 2024, we take a deeper dive on "second-generation" I&I markets, including lupus, alopecia, and vitiligo, which have limited treatment options and could contribute materially to topline growth, but remain elusive markets given disease-specific challenges.

Exhibit 53: Upcoming I&I launches
We could see additional market disruption with additional launches YE23 / 2024

Company	Therapy	Target/MOA	Form	Indication	Phase	Expected launch timeline
AbbVie	Skyrizi	IL-23	Injectable	Ulcerative Colitis	Submitted	2024 commercial launch
Pfizer	Velsipity	S1P	Oral	Ulcerative Colitis	Approved	YE23 commercial launch
Pfizer	Litfulo	JAK	Oral	Alopecia	Approved	YE23 commercial launch
Eli Lilly	Lebrikizumab	IL-13	Injectable	Atopic Dermatitis	Submitted	Pending CRL, 2024 launch
Eli Lilly	Omvah	IL-23	Injectable	Ulcerative Colitis	Approved	2023-2024 commercial launch

Source: Company reports; BofA Global Research

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For our latest outlook on the state of the I&I market, including proprietary BrandImpact data (see our September 2023 BrandImpact updates); also, feel free to ask us for our Global I&I Market Model.

Systemic Lupus Erythematosus (SLE) – unmet need clouded by trial failures.

SLE, the most common type of lupus, is a complex, autoimmune disease that can affect joints, skin, brain, lungs, kidneys, and blood vessels. Currently, there is no cure for SLE, and treatment today primarily consists of symptom management with the goal of reducing inflammation, slowing down disease progression, and preventing flare-ups. We'd note that there are three primary presentations of SLE: rash, arthritis, and kidney disease. Most patients are treated with a combination of drugs, namely hydroxychloroquine, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (e.g., prednisone), and immunosuppressants. While disease management has come a long way, persistent disease presentation despite background conventional treatment with corticosteroids and immunosuppressants is common, though not well-characterized given the heterogeneity of patients. Biologics are typically used as a later line therapy for patients whose disease is not sufficiently controlled by conventional drugs. By our most conservative estimates using clinical trial data, we'd estimate that the global addressable patient population for biologic therapy is between 40-45 thousand with an upper limit of nearly 300 thousand SLE patients (Exhibit 54). We'd also add that treatment is chronic and lifetime per patient revenue could be significant.

Exhibit 54: SLE Market Model
Sizing the SLE market is challenging given heterogenous patient presentation and treatment sequencing

SLE Market Model

US Market	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
SLE prevalence, adult (,000s)	206	207	207	208	208	208	209	209	209	209	209	210
Growth (%)	0.5%	0.4%	0.3%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with moderate to severe SLE (%)	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%
Patients uncontrolled by current therapy / have high disease activity (%)	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Addressable adult population (,000s)	16	16	16	16	16	16	16	16	16	16	16	16
OUS Market (EU + Japan)	**2019**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**	**2025E**	**2026E**	**2027E**	**2028E**	**2029E**	**2030E**
SLE prevalence, adult (,000s)	324	324	324	325	325	325	326	326	326	326	327	327
Growth (%)	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with severe SLE (%)	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%	51%
Patients uncontrolled by current therapy / have high disease activity (%)	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Addressable adult population (,000s)	25	25	25	25	25	25	25	25	25	25	25	25
Global addressable adult population (,000s)	41	41	41	41	41	41	41	41	41	41	41	41

Source: BofA Global Research estimates; Arthritis Rheumatol. 2021 Jun; 73(6): 991–996., Nat Rev Rheumatol. 2021 Oct;17(10):642., Rheumatology (Oxford). 2020 Mar; 59(3): 495–504

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That said, only a couple of biologics have been approved to treat SLE, namely GSK's Benlysta (belimumab, approved in 2011) and AstraZeneca's Saphnelo (anifrolumab,

approved in 2021). Rituximab is also commonly used to treat SLE as well, as per our KOL checks, albeit off-label. That said, only a couple of biologics have been approved to treat SLE, namely GSK's Benlysta (belimumab, approved in 2011) and AstraZeneca's Saphnelo (anifrolumab, approved in 2021). Rituximab is also commonly used to treat SLE as well, albeit off-label.

A number of JAK/TYK inhibitors have been studied as a potential treatment for SLE with mixed results. Lilly's Olumiant (baricitinib), Pfizer/Priovant's brepocitinib, and Nektar's Rezpeg (rezpegaldesleukin) are recent examples of biologics that have had inconclusive clinical trial results in SLE.

> *"But again, lupus trials and lupus therapies as you can well imagine, are very difficult to do and to get the results we're looking for. I know BMS is looking at the deucravactinib in lupus trial — those trials take a long time, and we'll see."*

Exhibit 55: Summary of biologics clinical development in SLE
Clinical development of biologics for the treatment of SLE has been challenging

Biologic Drugs	Trade Name	Mechanism of Action	Target	Status
rituximab	Rituxan	B cell targeted	CD20	Off-label use
belimumab	Benlysta	B cell targeted	BAFF, APRIL	Approved
anifrolumab	Saphnelo	Interferon I receptor antagonist	Interferon I receptor	Approved
baricitinib	Olumiant	Janus kinase inhibitor	JAK1/JAK2	Clinical development discontinued following mixed phase 3 results
brepocitinib	N/A	dual JAK1/TYK2 inhibitor	JAK1/TYK2	Clinical development discontinued due to failure to meet primary endpoint in phase 2
rezpegaldesleukin	Rezpeg	Regulatory T-cell (Treg)	IL2	Clinical development discontinued due to failure to meet primary endpoint in phase 2
upadicitinib	Rinvoq	Janus kinase inhibitor	JAK1	Clinical development to continue in phase 3 trials
deucravicitinib	Sotyktu	TYK2 inhibitor	TYK2	Clinical development to continue in phase 3 trials

Source: Company reports, BofA Global Research

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Feedback from KOLs, however, suggest that clinical trial design, patient selection, high placebo treatment effect, and/or drug dose may have been factors in prior clinical trial failures, and should not necessarily cloud the potential benefits of inhibiting the JAK/STAT pathway as a therapeutic modality in SLE. We'd note that the biological basis for targeting JAK1/TYK2 remains one of the more promising as JAK1 and TYK2 directly interact with Type 1 interferon (IFN), a powerful immune adjuvant upregulated in SLE patients.

Exhibit 56: JAK-mediated signal transduction
JAKs mediate signal transduction for a variety of cytokines involved in inflammatory conditions

	IL-2	IFN-γ	Type 1 IFN	IL-12	IL-23	IL-6	GM-CSF/Epo
JAK1	+	+	+	-	-	+	-
JAK2	-	+	-	+	+	+	+
JAK3	+	-	-	-	-	-	-
TYK2	-	-	+	+	+	+	-

Source: adapted from *Nature Reviews Drug Discovery* volume 16, pages843–862 (2017)

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Despite prior clinical trial failures and challenges in drug development, we maintain that phase 2 data are supportive of continued development of Rinvoq and Sotyktu for SLE.

Compared to prior drugs that have failed, Rinvoq and Sotyktu are more selective inhibitors of their respective targets, JAK1 and TYK2. That said, we'd note that there were some confounding factors in the phase 2 datasets, namely: Rinvoq did not achieve a stat sig difference in SRI-4 compared to placebo, and Sotyku did not demonstrate a dose-dependent response.

Exhibit 57: 48-Week composite SLE data, normalized to placebo
Note the limitations of cross-trial comparisons. Both Rinvoq and Sotyktu met their phase 2 primary endpoints as predetermined by the companies.

Company	Abbvie		Bristol Myers Squibb		AstraZeneca
Trial	Sleek (Ph2, NCT03978520)		Ph2b (NCT03252587)		Ph3 (NCT02446899)
Asset	Rinvoq (30 mg)	Sotyktu (3 mg BID)	Sotyktu (6 mg BID)	Sotyktu (12 mg QD)	Saphnelo
Pbo-adj SRI-4 and steroid dose ≤10mg QD at 48wk (%)	13.4	22.7	12.9	12.8	-
p value	0.075	<0.001			-
Pbo-adj Bicla* (%) at 48 wk (%)	30.8	21.7	9.9	10.4	16.3
p value	<0.001	0.001			0.001

Source: Company reports, BofA Global Research

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Overall, we think approval of additional biologics could shift the treatment paradigm in SLE given the high unmet need, and limited treatment options, but caution read-through in early clinical development given prior clinical trial failures and ongoing challenges in identifying patients for targeted therapy approaches.

Alopecia Areata – KOLs suggest that uptake will likely be robust

Alopecia areata (AA) is a nonscarring autoimmune disorder characterized by hair loss. While benign, our KOLs note that the emotional and mental toll of moderate-severe cases drives many patients to seek treatment. While AA is common, affecting approximately 160 million globally, and over 6 million people in the U.S., patients treated for alopecia represent a far smaller number though, given the wide variation in disease presentation. The first-line treatment for most patients with patchy AA is a topical corticosteroid (~80%), followed by oral steroids (~30%) as a secondary treatment.

Exhibit 58: Alopecia areata market model
While AA is common, affecting approximately 160 million globally, and over 6 million people in the U.S., patients treated for alopecia represent a far smaller number

Alopecia Areata (AA) Market Model	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US Market	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
AA prevalence, adult (,000s)	6,592	6,618	6,638	6,651	6,658	6,665	6,671	6,678	6,685	6,691	6,698	6,705
Growth (%)	0.5%	0.4%	0.3%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with moderate-to-severe AA	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
Patients with spontaneous regrowth within 1-year	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Patients treated for AA	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Addressable adult population (,000s)	288	290	290	291	291	292	292	292	292	293	293	293
OUS Market (EU + Japan)	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
AA prevalence, adult (,000s)	129,740	129,870	130,000	130,130	130,260	130,390	130,520	130,651	130,782	130,912	131,043	131,174
Growth (%)	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with moderate-to-severe AA	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
Patients with spontaneous regrowth within 1-year	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Patients treated for AA	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%	25%
Addressable adult population (,000s)	5,676	5,682	5,687	5,693	5,699	5,705	5,710	5,716	5,722	5,727	5,733	5,739
Global addressable adult population (,000s)	5,965	5,971	5,978	5,984	5,990	5,996	6,002	6,008	6,014	6,020	6,026	6,032

Source: BofA Global Research estimates; JAMA Dermatol. 2023 Apr; 159(4): 411–418., Adv Ther. 2021; 38(9): 4646–4658.

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Currently, two JAKi, Lilly's Olumiant (2022) and Pfizer's Litfulo (2023), are approved for the treatment of AA with a list price of $24,000-49,000 ($36,500) annually. By our estimates, in the U.S. alone, the market opportunity for alopecia could exceed $1B, assuming a mid-point, annual net price of $20,000 and >50,000 patients treated. Currently, biologics are prescribed to <1% of patients, but potentially represent a significant market opportunity.

That said, we caveat that safety is a concern for prescribers, especially given that alopecia is an otherwise benign condition. On Sotyktu:

> *"They're looking for approval of that to compete with baricitinib or Olumiant in alopecia areata. And their numbers look good. Again, they're going to face the same kind of uphill battle on with label and side effect profile that baricitinib has. But efficacy-wise, it looks very good, again, comparable to the type of results that we see with baricitinib."*

Overall, we view alopecia areata as one of the more promising next generation I&I markets with both a sizeable patient population and revenue growth potential.

Vitiligo – high prevalence, though treatment needs are unclear

Vitiligo is an autoimmune condition that leads to the de-pigmentation of the skin and has multiple presentations. The most commonly treated form of vitiligo is generalized, nonsegmental vitiligo, which is characterized by patches that present bilaterally and is unpredictable in its spread (as opposed to segmental vitiligo, which spreads rapidly, but stabilizes within 2-3 years). Vitiligo prevalence is not well-documented given the lack of formal diagnoses. As our KOLs have noted, the demand for treatment is relatively low given its benign nature and evolving societal acceptance of the condition. Still, we see higher demand in regions where vitiligo may still be stigmatized and for a subset of people whose vitiligo is detrimental to their quality of life. We highlight biologics that have progressed in clinical development below:

Exhibit 59: Biologics in development for the treatment of vitiligo
There are no approved systemic biologic therapies for the treatment of vitiligo.

Biologic Drug	Trade Name	Mode of Action	Target	Status
ruxolitinib 1.5%	Opzelura	topical Janus kinase inhibitor	JAK 1/2	approved
ritlectinib	Litfulo	Janus / tyrosine kinase inhibitor	JAK3/TEC	Phase 3 trial ongoing
povorcitinib	N/A	Janus kinase inhibitor	JAK1	clinical development to continue in phase 3
upadicitinib	Rinvoq	Janus kinase inhibitor	JAK1	clinical development to continue in phase 3
afamelanotide	Scenesse	melanocortin 1 receptor agonist	MC1R	Phase 3 trial ongoing

Source: Company reports

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By our estimates, we think fewer than 5% of patients are likely to seek treatment despite the relatively large market size overall.

Exhibit 60: Vitiligo market model
Despite relatively high prevalence of vitiligo, number of patients seeking therapy is limited due to limited formal diagnoses rates and changing societal perceptions

Vitiligo Market Model	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
US Market	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Vitiligo prevalence, adult (,000s)	1,978	1,985	1,991	1,995	1,997	1,999	2,001	2,003	2,005	2,007	2,009	2,011
Growth (%)	0.5%	0.4%	0.3%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with non-segmental vitiligo (%)	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%
Patients seeking therapy (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Addressable adult population (,000s)	84	84	85	85	85	85	85	85	85	85	85	85
OUS Market (EU + Japan)	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Vitiligo prevalence, adult (,000s)	3,968	3,972	3,976	3,980	3,984	3,988	3,992	3,996	4,000	4,004	4,008	4,012
Growth (%)	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Patients with non-segmental vitiligo (%)	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%	85%
Patients seeking therapy (%)	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Addressable adult population (,000s)	169	169	169	169	169	169	170	170	170	170	170	171
Global addressable adult population (,000s)	253	253	254	254	254	254	255	255	255	255	256	256

Source: BofA Global research estimates; JAMA Dermatol. 2022 Jan; 158(1): 1–9., J Eur Acad Dermatol Venereol. 2022 Oct;36(10):1831-1844

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That said, we note that there are no systemic biologics currently approved for treatment but could see some demand given high efficacy observed in phase 2 trials. In particular, we call out recent data from AbbVie's Rinvoq and Incyte's povorcitinib. We think vitiligo

adds modest tailwinds to Rinvoq's peak sales potential, if approved, at most and do not view it as a substantial contributor to peak sales.

Exhibit 61: Rinvoq and Povortitinib phase 2b data

While there are no systemic biologics currently approved for vitiligo but could see some demand given high efficacy observed in phase 2 trials.

Company	AbbVie				Incyte			
Trial	phase 2b (NCT04927975)				phase 2b (NCT04818346)			
Asset	Rinvoq				povorcitinib			
	UPA 6 mg	UPA 11 mg	UPA 22 mg	PBO	15 mg	45 mg	75 mg	PBO
Percent CFB in F-VASI	-22	-35.6	-34.0	-14.4	-27.7	-36.4	-29.4	-5.1
Diff vs PBO (p-value)	-7.6 (p=0.304)	-21.3 (p=0.005)	-19.6 (p=0.013)		-22.6	-31.3	-24.3	
F-VASI 75 (%)	8.2	19.1	14	2.2	13.2	18.2	13.9	3
Diff vs PBO (p-value)	6.9 (p=0.100)	17.8 (p=0.002)	11.7 (p=0.026)		10.2	15.2	10.9	
T-VASI 50 (%)	6.1	6.4	11.6	2.2	10.5	15.2	5.6	3
Diff vs PBO (p-value)	3.7 (p=0.340)	3.8 (p=0.358)	9.1 (p=0.027)		7.5	12.2	2.6	

Source: Company reports

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Top 25 Catalysts to Watch in 2024

1. **Lilly – Tirzepatide Phase 2 NASH readout (1Q24):** While the obesity momentum was strong in 2023, we expect label expansion opportunities to be in focus in 2024, particularly as we get more clarity on access + reimbursement for obesity. Indeed, we think Lilly and Novo's 'backdoor' strategy of targeting other metabolic diseases makes a lot of sense to broaden the total addressable market for the GLP-1 class, especially as related co-morbidities in some cases have straightforward reimbursement pathways. For tirzepatide in NASH, we should receive results in 1Q which we expect to support continued pivotal development based on the totality of metabolic benefit. Recall that Novo's semaglutide (0.4mg once a day) at 72 weeks in non-cirrhotic patients showed a 10% placebo-adjusted improvement in ≥1 stage fibrosis with no worsening of NASH (secondary endpoint for trial) as compared to 20% for 89Bio's pegozafermin (44mg once every 2 weeks) at 24 weeks. The primary endpoint for the trial is the percentage of participants with absence of NASH with no worsening of fibrosis on liver histology at 52 weeks. Recall, at 72 weeks, Novo's semaglutide showed 44% benefit (3.5x improvement as compared to placebo) versus at 24 weeks, a 24% benefit (13.5x improvement) for 89Bio's pegozafermin (44mg once every 2 weeks). So, in our view, if tirzepatide looks comparable or numerically superior to NASH players 89Bio or Akero, we think the Street would view the results favorably.

2. **Lilly – donanemab full regulatory approval (1Q24)**: Investors haven't focused on donanemab for Alzheimer's as much as tirzepatide for obesity + related comorbidities, which makes sense as the commercial opportunity isn't as broad. That said, we should receive a regulatory decision for donanemab in Alzheimer's in 1Q24, following a disclosure that the PDUFA was pushed from late 2023 which has investors nervous on the possibility of a complete response letter (CRL) following the accelerated approval CRL last year (see our thoughts on donanemab's CRL here). When we caught up with Lilly, management noted FDA needed more time to look at the entirety of the package (e.g., full safety and efficacy), as it was a very large submission, but management was clear there weren't any concerns on safety of efficacy. We're not concerned with this delay, as now that one Alzheimer's drug is approved, FDA can be more particular on the package and label, in our view. On that note, we expect the donanemab's label to be comparable to Biogen's Leqembi, including a black box warning for Amyloid-related imaging abnormalities (ARIA). However, we don't know how the label will reflect donanemab's dosing strategy (e.g., finite dosing or will it be up to the prescribers) or the patient population (e.g., will the label exclude low and high tau patients). Indeed, in our view, these points will be important as we consider donanemab's launch in Alzheimer's in 2024.

3. **Vertex – VX-548 phase 3 results in acute pain (early 2024):** Following the robust phase 2 results for VX-548 in diabetic peripheral neuropathy late last fall (see our thoughts on VX-548's results here), we think expectations are high for VX-548 in acute pain. Recall, we will receive results for VX-548's three phase 3's to look at improvements in pain following bunionectomy + abdominoplasty and a single-arm safety and efficacy study in acute pain to support a broad, moderate-to-severe acute pain label. In terms of what to expect in the trial, we suspect if results recapitulate what was seen in the phase 2 trial, the results will be viewed as a homerun. That said, as we mentioned in the pain section above, we suspect that commercial hurdles will slow the launch + limit the commercial opportunity based on our channel checks, which is why we remain below the Street's forecasts in acute pain.

4. **Vertex – vanzacaftor, Vertex's next generation Cystic fibrosis (CF) triple, phase 3 results (early 2024):** We expect Vertex to present the phase 3 results for it's next-generation CF triple, vanzacaftor, to support a regulatory submission in early 2024. Given Trikafta's dominance in the space, we've gotten a few inbounds on how much better could vanzacaftor be? We thought Vertex has done a good job highlighting its differentiation, namely 1) vanzacaftor is a once a day pill as compared to twice a day for Trikafta, which could increases convenience and therefore potential compliance, 2) a potentially improved tolerability profile, so patients that discontinued Trikafta may restart treatment, and 3) importantly, potentially greater improvements in cystic fibrosis transmembrane conductance regulator (CFTR) function based on the phase 2 trials (e.g., lower levels of sweat chloride) and in vitro results from human bronchial epithelial (HBE) assays (e.g., improved chloride transport in vitro), which typically have strong translation from the bench to the clinic. Moreover, vanzacaftor likely carries a substantially lower royalty burden than Trikafta, which in addition to the potential to increase its price over Trikafta, creates more favorable economics for the additional 6k patients who are eligible for CFTR modulators. Quotes from Vertex management from their 1Q earnings call *"So on vanzacaftor, just to remind everybody on the call, our goal in cystic fibrosis is to get as many people as possible to carrier levels of chloride transport as we can. Carryovers of sweat chloride, pardon me, as we can because we believe if we can do that, we will essentially be able to prevent CF developing in people as we know it today. As you know, from our in-vitro assays, but also from our clinical data with the vanzacaftor triple combination, we believe we can get to even higher levels than we've even been able to establish with TRIKAFTA which, as you know, so it's a very, very high bar. And so, the study that we have ongoing, both in 12 plus but also is our 6 to 11 is aimed to do just that, to compare TRIKAFTA with vanzacaftor. And obviously, we were looking forward to seeing the data when those studies read out."*

5. **Moderna – mRNA-1647 phase 3 vaccine results in Cytomegalovirus (CMV) (mid 2024):** Following Moderna's disclosure that its phase 3 trial for mRNA-1647 evaluating the efficacy + safety of the vaccine in women of childbearing age, including adolescents, was fully enrolled and accruing cases (25% accrued as of September), we expect interim results in mid-2024 with the next update likely at Moderna's Vaccine Day in the spring. For the interim look, Moderna needs 81 cases to perform the first analysis, with a vaccine efficacy bound of 57.7%, if Moderna beats this objective, they trial may be stopped early. If not, it wouldn't necessarily mean that the vaccine wouldn't hit the primary endpoint, just the case split wasn't powerful enough to conclude the study. Ultimately, we suspect it's likely that Moderna will be successful based on our channel checks, but it's unclear if the trial will be well powered enough to detect a meaningful difference at the first interim analysis. Recall, CMV is the most common congenital infection worldwide with >$1B in annual healthcare costs, so there's a high unmet need in the space. Indeed, we suspect the commercial opportunity could be meaningful but will likely take some time to ramp, comparable other latent disease vaccine launches.

6. **BioMarin – Roctavian global launch in severe hemophilia A:** While Roctavian's launch in Germany + the US has been slower than expected given commercial hurdles and the high price point, we expect the launch to inflect looking to 2024 now that we have a final price set in Germany + a J-code in US. Indeed, while only 2 patients have been treated in Germany, we attribute this to a lack of a final price versus a lack of patient demand, which remains high according to our KOLs. We forecast sales of $453M as compared to $167M for the Street, which we don't think is heroic as it only implies 355 patients versus 130 patients for the Street. That said, we wouldn't be surprised if patient

uptake is backloaded to 2H24, as prescribers + patients get comfortable with the new modality.

7. **Biogen – Leqembi ongoing launch in Alzheimer's (2024):** Leqembi's ongoing launch in Alzheimer's has been slow, in-line with expectations, with 800 patients treated as of the 3Q print (see our thoughts on the earnings print now). That said, Biogen + Eisai have guided to 10K patients on treatment by the end of 1Q24, but investors remain skeptical of the company's ability to hit this benchmark, more likely only 5-7K patients. Indeed, KOLs that we have spoken to have been split on the likelihood of hitting 10K patients given commercial hurdles (e.g., PET imaging + MRI requirements, lack of neurologists and ARIA), with the more important outlook what real-world safety + tolerability looks like. Notably, ARIA typically occurs within the first couple months of treatment and if 5-10K patients initiate Leqembi treatment, we should get an accurate picture of its real-world safety profile + prescribers experience with adverse events (AEs). Based on our KOL discussions, if there are patient deaths in the real-world comparable to what was seen in Leqembi's open label extension, FDA may add an additional black box warning highlighting the potential for death. If this occurs, we'd see it as a meaningful overhang for both Leqembi and Lilly's donanemab.

8. **Vertex/ CRISPR – Casgevy commercial launch in Sickle cell disease (SCD) and approval/ launch in Transfusion-dependent beta-thalassemia (TDT) (1H24):** We suspect Casgevy's commercial launch inflection will take time as the patient journey to receive Casgevy is quite time consuming and onerous with the busulfan conditioning regimen. Indeed, the journey can be characterized as 1) a screening period, 2) a pre-treatment period, 3) manufacturing period, and 4) treatment period, which is a multi-month process that needs to be scheduled ahead of time. That said, Vertex + CRISPR have already activated multiple authorized treatment centers which are required as Casgevy treatment necessitates specialized experience in stem cell transplantation, which is important as we assess potential patient uptake. Notably, we expect Casgevy's price of $2.2M to be viewed favorably by payers + prescribers as its a steep discount to competitor BlueBird's (covered by Jason Gerberry) Lyfgenia, a lentiviral gene therapy, with a price of $3.1M. We'd also say CRISPR + Vertex have done a job setting expectations for the launch, but even the Street's forecast of ~$162M (BofA $166M) could be challenging to hit if we look at precedent from other curative intent gene therapy launches (e.g., BioMarin's Roctavian for severe hemophilia A).

9. **Pfizer / Moderna – US stockpiling of RSV vaccines and maternal/pediatric RSV launch (2024)** – Following year-end announcements that the Biden administration had negotiated with manufacturers to make an additional 230,000 doses of RSV immunizations for infants available in January 2024, we are incrementally more bullish on the maternal / pediatrics RSV market in the US. Already, we had revised our estimates given robust uptake in the US adult population supported by $0 co-pay for Medicare part D beneficiaries and incentivized for $0 co-pay with Medicaid beneficiaries (maternal / pediatric population), if recommended by ACIP. While we think GSK will maintain its lead in the adult RSV market, driven by its DTC retail exposure through pharmacies (GSK maintains majority share at retail pharmacies with >90% scripts coming from the retail setting), we could see Pfizer uptake in the maternal / pediatrics RSV market come out on top, driven by Pfizer's primary care salesforce penetration. Moderna's RSV vaccine is also expected to receive approval in 2H24. Given its potentially best-in-class safety profile (no Guillian Barr Syndrome). Moderna's RSV vaccine could potentially take meaningful shares from Pfizer/ GSK if it receives a full recommendation as opposed to shared clinical decision recommendation that Pfizer/GSK have.

10. **Gilead – lenacapavir combination data from the pivotal PURPOSE program (YE24):** Ultimately, the biggest opportunity for longer-acting formulations for HIV are likely to come from PrEP vs. the treatment market. While few KOLs expect any issues on the clinical front, we remain tuned into the commercial challenges ahead for Gilead, and believe data and market exposure through the PURPOSE program may help support uptake beyond the current 25% penetration rates (of ~1.2 million eligible). The PURPOSE 1 trial completed enrollment of >5,300 cisgender adolescent girls and young women ages 16-25 in South Africa and Uganda in September 2024 (YE24 data), while the PURPOSE 2 trial enrolled >3,200 of cisgender men who have sex with partners assigned male at birth in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the United States (2025 data). Already, we see slowing adoption of GSK's Apretude for PrEP (see our 3Q23 GSK read through note), which we suspect is due to switching hesitancy beyond early adopters and think the broader market exposure of the PURPOSE trials and lenacapavir's longer dosing interval (every 6 months, Q6M) should support robust uptake beginning 2025, pending approval.

11. **Regeneron – Linvoseltamab and odronextamab commercial launch and impact on competitive landscape (2024):** With filing underway for linvoseltamab and filing completed for odronextamab, and approval likely for both, commercial execution will be key for Regeneron as the company looks to diversify its revenue concentration risk. Overall, we are incrementally more positive about the commercial prospects for linvoseltamab in r/r MM given data suggestive of better response rates and lower CRS, though we maintain that the treatment landscape in r/r MM is competitive and gaining share remains challenging. Linvoseltamab would be competing with J&J's Tecvayli and Pfizer's Elrexfio, and we're looking to understand how much treatment convenience deters uptake. Separately, we maintain that commercialization of odronextamab in DLBCL could be challenging for Regeneron as both Roche's Columvi (fixed dose IV) and AbbVie / GenMab's Epkinly (SC) have first-to-market advantages. See our note on Regeneron's ASH 2023 updates.

12. **US Biopharma – IRA Drug Price Negotiation Program MFP (September):** CMS will publish the maximum fair prices (MFP) of the initial 10 drugs selected for the IRA Drug Price Negotiation Program on September 1st (initial offers in February), effective in 2026. Prior guidance indicated that at a minimum, manufacturers should expect >25% discount for drugs marketed 9-16 years (8/10 drugs) and >60% discount for drugs marketed >16 years (2/10 drugs). Overall, negotiated prices must be less than what Medicare currently pays less manufacturer discounts and rebates (4-60%). We'd note that Merck (11/21/23), Bristol (12/8/23), and Janssen (12/8/23) have filed lawsuits, so the IRA may be subject to further amendments or potentially a temporary injunction. That said, initial prices published in February will set the tone on future discounting.

13. **Regeneron – Mylan/Viatris Eylea patent litigation final outcome and read-through on LOE (2H24):** REGN shares traded with strength following announcement that the company had successfully defended key Eylea patents in its ongoing lawsuit against Mylan/Viatris. While the announcement was undoubtedly a win for Regeneron, we think there is still wood to chop before read-through to the May 2024 LOE is decided.

    We'd note a few caveats underappreciated by the Street: 1) The judge's ruling relates only to Mylan/Viatris. Although we suspect Regeneron plans to sue other biosimilar companies for patent infringement, these are separate processes and may have different outcomes based on the specific patents brought to trial (outside of '865, '601, and '574). 2) There will still be an appeals process whereby Regeneron would seek a statutory injunction to uphold the judge's

ruling (e.g., prevent the Mylan/Viatris from launching). However, we think it is unlikely that Regeneron will be able to secure a statutory injunction by May 2024 (essentially the appeals process would need to conclude in 4.5 months). 3) Overall, we don't think the judge's ruling on the Mylan/Viatris case necessarily suggests that Eylea's LOE will be extended to June 2027 ('865 patent expiry). Indeed, we maintain that best case, Regeneron seeks to settle on a biosimilar launch date sometime in 2026 with multiple companies and look for additional updates during 1H24.

14. **AbbVie/ Cerevel / Bristol / Karuna / Neumora – KarXT approval in schizophrenia (September) and pivotal emraclidine data (2H24):** We'd note that despite preference for generics in the treatment of psychiatric disorders, a branded product could still command leading market share if sufficiently differentiated. Indeed, we think muscarinic receptors offer improved efficacy and a favorable tolerability tradeoff. As such, we are overall bullish about the drug class. Furthermore, if Cerevel's (AbbVie) emraclidine demonstrates comparable efficacy with KarXT in pivotal trials (2H24), KarXT my face commercial challenges. Recall that emraclidine may have best-in-class tolerability (minimizing GI related side effects) as well as convenience as a once-daily pill with no titration needed vs. Karuna's KarXT. Separately, given the similarity between Neumora's NMRA-266 and emraclidine, positive results from emraclidine should bode well for Neumora as well.

15. **AbbVie/ ImmunoGen – PICCOLO full data to support label expansion of Elahere into PSOC (mid-2024):** While ImmunoGen's Elahere is already approved for the treatment of 2L+, FRa high platinum-resistant ovarian cancer (PROC), we think there is strong upside potential (doubling of patient population with PSOC FRa med/low expression, and longer treatment duration) with additional label expansion into the earlier and platinum-sensitive settings (PSOC). Immunogen is currently running trials in 3L+ PSOC FRa high (PICCOLO) and 2L maintenance FRa high (GLORIOSA) settings, with PICCOLO's full data expected in mid-2024 and GLORIOSA still enrolling. We think positive data would validate AbbVie's premium paid for ImmunoGen, and further supports potential of ADC's in transforming the treatment paradigm of solid tumors.

16. **AbbVie – Navitoclax filing in myelofibrosis and additional data on disease modification biomarkers (1H24):** Both AbbVie's BCL-XL inhibitor navitoclax (NAV) in TRANSFORM-1 and MorphoSys's BET inhibitor pelabresib (PELA) in MANIFEST-2 in 1L JAKi-naïve myelofibrosis patients had mixed efficacy data, failing to show statistically significant improvement in total symptom score (TSS) compared to ruxolitinib (RUX) + placebo (PBO) in 1L MF despite positive results based on the primary endpoint, SVR35 (see our ASH 2023 myelofibrosis update note). As such, we think that neither combination has a clear advantage yet, and further analysis is warranted. On safety, PELA+RUX, there were fewer grade 3 events. We are looking for an update on disease modification biomarkers from TRANSFORM-1 is pending, and likely will not be available until 2024, but could make the NAV+RUX combination more attractive despite some increased toxicity. Navitoclax would help further diversify AbbVie's declining heme/onc franchise.

17. **Bristol / Merck / Gilead – Opdualag phase 2 1L NSCLC data (1Q24) and 1L HCC (2024) and Skyscraper-01 OS data (1Q24).** Opdualag has been a key growth for Bristol in the melanoma space. That said, it had experienced set back recently in 2L HCC (liver cancer) and it remains to be seen whether PD-1/LAG-3 combo can demonstrate superior results in 1L NSCLC. Indeed, positive Opdualag results could bolster both Bristol and Merck outlook on extending their respective IO franchise as Merck also has LAG-3 (favezelimab) in development. Separately, TIGIT remains a hot topic heading into 1Q24 with

Skyscraper-01 OS data expected to readout soon. In our view, a positive OS result could bolster all TIGIT players.

18. **Amylyx – TUDCA-ALS data (January) and confirmatory PHOENIX readout (2Q24).** While management does not think TUDCA-ALS, which evaluates one of Relyvrio's components, should be used as a read-through to PHOENIX, investors we've talked to generally view an overwhelming positive TUDCA-ALS outcome as a potential threat given it may put pressure on Relyvrio's net pricing in Europe (but no impact to the US market). On the other hand, a negative readout may dampen the investors' confidence on PHOENIX's potential success. The best-case scenario, according to investors, is that the trial barely misses stat sig. while showing a positive trend, which would give investors more confidence on PHOENIX readout. That said, given TUDCA-ALS trial was conducted during COVID, a smaller number of trial participants were enrolled, which could be further reduced due to COVID drop out, making it difficult to draw conclusion and read-through to PHOENIX. That said, ultimately a positive PHOENIX readout is a necessary condition for AMLX shares to inflect, making Amylyx a top M&A target.

19. **Merck – Sotatercept approval/ launch for PAH (March 26).** Sotatercept approval (PDUFA March 26) in PAH and a fast uptake could bolster CV portfolio outlook. Our KOLs think sotatercept brings differentiated benefit to PAH patients, which should drive strong demand. We model sotatercept 2030 revenue at $4.4B vs. $4.5B consensus.

20. **Merck / Gilead/ AbbVie/ J&J Teliso-V – ADC updates from phase 2 LUMINOSITY in cMET NSCLC (ASCO), Trodelvy EVOKE-01 2L+ NSCLC (1H24), and HER3-DXd approval/launch EGFR 2L+ NSCLC (June 24).** We expect to see numerous updates from ADCs in 2024, including potential approval and launch of HER3-DXd in EGFR 2L+ NSCLC, which will likely compete directly with J&J's Rybrevant/lazertinib in the post-Tagrisso setting. On the other hand, Trodelvy will show first phase 3 data in 2L+ NSCLC, which investors will look to compare results with Dato-DXd's TROPION-Lung01. Separately, AbbVie's Teliso-V is also looking to take shares in the 2L+ NSCLC by segregating out the cMET expression patients. Full data will be presented at ASCO and AbbVie plans to file for accelerated approval in fall 2024.

21. **Gilead / Merck – ADC updates from Dato-DXd TROPION-Breast02 1L TNBC (2H24). Trodelvy TROPiCs-04 2L UC (2H24) and TROPHY U-O1 1L UC (2H24).** Outside of lung cancer, we expect to see important data update in in breast and urothelial cancers, providing first look into opportunities on indication expansions into earlier treatment settings. Indeed, success in these trials would represent significant market opportunities and drive further interests into the field.

22. **Bristol Myers / Cytokinetics – MYK-224 phase 2 MERCUTIO data in oHCM (mid-24), aficamten SEQUOIA full data (ASCO).** While SEQUOIA's topline data look impressive, questions remain on whether aficamten is the "next-" or "best-in-class" at this point until we see full data at ASCO 2024. Indeed, experts we spoke with largely agreed that 1) the molecules are more similar than not, and 2) aficamten is unlikely to escape the onerous REMS that has slowed Camzyos' uptake. Importantly, given Bristol's next-gen myosin inhibitor MYK-224, which has a shorter half-life vs. Camzyo, phase 2 data are expected to readout in mid-2024, it remains to be seen how the field will play out ultimately.

23. **Amgen – Obesity data from AMG786 (1H24) and AMG133 (2H24)** We see obesity to remain top of mind in 2024 given key data readouts, including Amgen's AMG133 phase 2 data, Lilly's BELIEVE bimagrumab phase 2b results,

and amylin phase 1 data from Lilly/Novo, as well as potential M&A. Indeed, we believe Amgen's obesity readouts will be key to share re-rating in 2H24. While AMG786 non-incretin data readout in 1H24 could be interesting, given management's 3Q23 commentary regarding treating AMG 786 as a "phase 1 asset with a novel mechanism-of-action," we think it's unlikely that a non-incretin-based agent could demonstrate a more favorable weight-loss/tolerability profile than a GLP-1 given the small sample size and short trial duration. On the other hand, we think AMG133 could be a potential game changer given its long-acting/once a month dosing frequency and compelling phase 1 results. The phase 2 data will be able to address long-term weight loss benefit and more importantly, safety and tolerability of the GIP antagonistic effect.

24. **J&J – nipocalimab phase 3 readouts in myasthenia gravis and warm autoimmune hemolytic anemia (early 2024).** While expectations are generally low for nipocalimab due to albumin binding/LDL safety concern, there may be an upside opportunity for the phase 3 readouts in myasthenia gravis and warm autoimmune hemolytic anemia in early 2024 if nipocalimab can demonstrate a competitive efficacy/safety profile vs. Argenx's Vyvgart.

25. **J&J / Neumora / AbbVie (Cerevel) - aticaprant phase 3 adjunctive MDD (mid-24) and navacaprant phase 3 MDD (2H24).** Navacaprant is a novel, oral once-daily, selective kappa opioid receptor (KOR) antagonist that has the potential to deliver attractive efficacy/tolerability profile compared to current antidepressant therapies (e.g. SSRIs, SNRIs) for MDD, which have undesirable side effects such as weight gain and sexual dysfunction with >50% of patients failed to respond. J&J's aticaprant, which shares the same MOA as navacaprant, is expected to report the first Phase 3 data in adjunctive MDD (VENTURA-1) in mid-2024, which will be a key read-through to navacaprant's phase 3 data in 2H24. Similarly, Cerevel's CVL-354 also targets KOR pathway for MDD. While it's still in early development, positive data from J&J and Neumora could bolster investor confidence on CVL-354's outlook.

Catalysts Across our Coverage to Watch in 2024

Major Pharma

Exhibit 62: Key major pharma potential catalysts in 2024

We've provided a list of company-specific potential catalysts to pay attention to in 2024

Company	Product	Indication	Phase	Readout	Timing
ABBV	Teliso-V	c-MET 2L+ NSCLC	Phase 2	Phase 2 data (LUMINOSITY) at ASCO	mid'24
ABBV	Teliso-V	c-MET 2L+ NSCLC	Regulatory	Submission for AA	2H24
ABBV	deal closures	N/A	Regulatory	Immunogen and Cerevel deal closures	mid-2024
ABBV / IMGN	Elahere	Frα platinum sensitive ovarian cancer	Phase 3	Full data from the PICCOLO study	mid-2024
ABBV / CERE	emraclidine	schizophrenia	Phase 2 / pivotal	Pivotal data	2H24
ABBV	Teliso-V	c-MET 2L+ NSCLC	Phase 3	Phase 3 confirmatory trial	TBD
ABBV	Navitoclax (BCL-2/XL)	1L myelofibrosis	Regulatory	Regulatory fililng and approval	2024
ABBV	Venclexta	MDS	Phase 3	VERONA trial readout; potentially ASH	YE24
ABBV	Botox	episodic migraine	Phase 3	Pivotal data supportive of Botox label expansion into episodic migraine prevention	2H24
BMY	KarXT	schizophrenia	Regulatory	next gen Camzyo (MERCUTIO)	9/26/24
BMY	Cerevel's emraclidine	schizophrenia	Pivotal	Two pivotal data in 2H24	2H24
BMY	RayzeBio	GEP-NETs	Phase 1	updated data	2H24
BMY	RayzeBio	SCLC	Phase 1	initial data	2H24
BMY	MYK-224	HFpEF	Phase 1	POC data	2024
BMY	MYK-224	oHCM	Phase 2	next gen Camzyo (MERCUTIO)	mid 2024
BMY	Cytokinetics' aficamten	oHCM	Phase 3	SEQUOIA-HCM full data at ASCO 2024	ASCO
BMY	cendakimab	EoE	Phase 3	Phase 3 data	2024
BMY	LPA1 antagonist	Pulmonary Fibrosis	Phase 3	Phase 3 data	2026+
BMY	Opdivo + chemo	1L UC	Regulatory	Priority review FDA PDUFA	5-Apr-24
BMY	Opdivo (+/- Yervoy)	HCC (1L)	Phase 3	1L HCC Data of CM-9DW	2024/2025
BMY	Opdivo (+/- Yervoy)	MSI High CRC (1L+)	Phase 3	Data of CM-8HW	2024/2025
BMY	Opdivo (+/- Yervoy)	Adj HCC	Phase 3	Data of CM-9DX	2024/2025
BMY	Opdivo (+/- Yervoy)	Peri-adj MIBC	Phase 3	Data of CM-078	2024/2025
BMY	Opdivo (+/- Yervoy)	Adj. NSCLC	Phase 3	Data of ANVIL, co-op group	2024/2025
BMY	Opdivo (+/- Yervoy)	NSCLC (Stage III)	Phase 3	Data of CM-73L (Stage III unresectable NSCLC)	2024/2025
BMY	subQ Opdivo	CM-67T	Regulatory	Filing in 2024 for approval; bridge 65-75% today's Opdiovo business/50% overall	2024/2025
BMY	Opdualag	NSCLC	Phase 2	Data of phase 2 study in 1L NSCLC; readout inearly 2024	early 2024
BMY	Opdualag	HCC (1L)	Phase 2	Data of phase 2 study in 1L HCC; 2L+ failed	2024
BMY	Opdualag	MSS mCRC(2L/3L+)	Phase 3	Data of phase 3 study	2024/2025
BMY	CD19 NEXT T	Lupus	Phaes 1	Phase 1 data	2024
BMY	Sotyktu	Lupus	Phase 3	Data of phase 3 (POETYK-SLE-1/-2)	2026
BMY	Sotyktu	Sjogren's	Phase 3	Data of phase 3 (POETYK-SjS-1)	2027
BMY	Sotyktu	PsA	Phase 3	Data of phase 3	2024/2025
BMY	Krazati (KRAS G12C)	NSCLC	Phase 3	2L NSCLC phase 3 confirmatory study; PFS data in 2024	2024
BMY	Krazati + Keytruda + chemo	NSCLC	Phase 2	1L NSCLC <50% TPS phase 2 data in 1H24 (KRYSTAL -17)	1H24
BMY	Krazati + cetuximab	CRC	Phase 3	2L CRC Phase 3 data expected in 2024	2024
BMY	Krazati + cetuximab	CRC	Regulatory	Phase 2 submission expected by YE 2023	2024
BMY	MRTX1712 (PRMT5/MTA)	Cancer	Phase 2	Phase 2 initiation in 1H24	1H24
JNJ	nipocalimab	Myasthenia Gravis	Phase 3	Data from phase 3 trial	early 2024
JNJ	nipocalimab	Warm Autoimmune Hemolytic Anemia	Phase 3	Data from phase 3 trial	early 2024
JNJ	Talquetamab (GPRC5DxCD3)	MM	Phase 3	MonumenTAL-5 trial vs. Blenrep in triple class refractory MM readout	2024

Exhibit 62: Key major pharma potential catalysts in 2024
We've provided a list of company-specific potential catalysts to pay attention to in 2024

Company	Product	Indication	Phase	Readout	Timing
JNJ / MGTX	AAV-RPGR	X-linked Retinitis Pigmentosa	Phase 3	Phase 3 Lumeos readout	2024
JNJ	JNJ-2113 (once daily)	Psoriasis	Phase 3	ICONIC-LEAD in moderate to severe plaque psoriasis	Nov '24 prim comp
JNJ	TARIS	MIBC	Phase 3	SunRise-1 durability results	2024
JNJ	Competitor CG Oncology	MIBC	Phase 3	BOND-03 durability results	2024
LLY	abemaciclib	Castrate-resistant prostate cancer	Phase 3	CYCLONE-2 readout- event driven	Early 2024
LLY	donanemab	AD	Approval	Full approval	1Q24
LLY	lebrikizumab	Atopic dermatitis	Regulatory	US approval post CRL	2024
LLY	orforglipron	Obesity/ T2D	Phase 3	Ongoing	2025 readouts
LLY	retatrutide	obesity/ T2D	Phase 3	Ongoing	2025 readouts
LLY	tirzepatide	Sleep apnea	Phase 3	SURMOUNT-OSA readout	Primary completion March 2024
LLY	tirzepatide	HFpEF	Phase 3	SUMMIT readout	Primary completion June 2024
LLY	tirzepatide	NASH	Phase 2	SYNERGY-NASH readout 1Q24	1Q24
Lilly	bimagrumab	Obesity	Phase 2	BELIEVE readout	mid-2024
MRK	favezelimab (anti-LAG-3)	PD-L1+ microsatellite-stable colorectal cancer	Phase 3	Phase 3 data in coformulation with Keytruda	2024
MRK	MK-2870 (TROP2 ADC)	solid tumors	Phase 2	Phase 2 data (Kelun trial)	2024
MRK	MK-2870 (TROP2 ADC)	TNBC	Phase 3	Positive topline announced (Kelun trial)	2024
MRK	Sotatercept	PAH	Regualtory decision	FDA action March 26, 2024	3/26/24
MRK	Sotatercept	HFpEF	Phase 2	Phase 2 CADENCE trial in Cpc-PH due to HFpEF	2024
MRK	Keytruda	Lung cancer	Phase 3	Data from phase 3 subcutaneous formulation vs IV formulation in combo with chemo in 1L NSCLC	2024
MRK	V116	pneumococcal vaccine (adult)	Regulatory decision	PDUFA on June 17, 2024	6/17/24
PFE	ford-mova	duchenne muscular dystrophy	Regulatory	FDA approval of gene therapy for DMD	2024
PFE	Talzenna + Xtandi	Metastatic castration sensitive prostate cancer	Phase 3	TALAPRO-3 data	2024
PFE	GBT-601	Sickle Cell Disease	Phase2/3	Potential NDA approval	2027
PFE	Inclacumab	Sickle Cell Disease	Phase 3	Potential BLA approval	2026
PFE (SGEN)	Tukysa	maintenance setting for HER2+ breast cancer	Phase 3	Pivotal combo data in the maintenance setting for HER2+ breast cancers from HER2CLIMB-05	4Q24
PFE (SGEN)	Tukysa	1L HER2+ colorectal cancer	Phase 3	Pivotal data in 1L HER2+ CRC from MOUNTAINEER-03	4Q25
PFE (SGEN)	Adcetris	DLBCL	Phase 3	Pivotal Adcetris data in DLBCL from ECHELON-03	4Q25

Source: BofA Global research, company data. Includes deals yet to complete.

BofA GLOBAL RESEARCH

Large Cap Biotechs

Exhibit 63: Key large-cap biotech catalysts expected in 2024

We've provided a list of company-specific catalysts to pay attention to for 2024

Company	Product	Indication	Phase	Readout	Timing
AMGN	AMG 133 (GLP1-GIP)	Obesity/ Diabetes	Phase 2	Phase 2 2023 start; topline data in late 2024	2H24
AMGN	AMG 786	Obesity	Phase 1	Small molecule non-incretin (target not disclosed)	1H24
AMGN	Tarlatamab (HLTE BiTE DLL3)	3L+ SCLC	Regulatory	DeLLphi-301	6/12/24
AMGN	Tarlatamab (HLTE BiTE DLL3)	2L SCLC	Phase 3	DeLLphi-304	2025
AMGN	Tezspire	COPD	Phase 2	Data readout in 1H24	1H24
AMGN	Rocatinlimab (OX40)	Atopic dermatitis	Phase 3	Rocket phase 3 readouts	2024/25
AMGG	AMGN 193 (PRMT5)	MTAP-null tumors	Phase 1/2	datate update	2024
AMGN	Uplizna (CD-19 mAb)	MG	Phase 3	Phase 3 MG data readout	2024
AMGN	Uplizna (CD-19 mAb)	IgG4-RD	Phase 3	Phase 3 IgG4-RD data readout	early 2024
AMGN	HZN-825 (oral LPAR1 antagonist)	IPF	Phase 2	Pivotal phase 2b trial	2024
AMGN	HZN-825 (oral LPAR1 antagonist)	dcSSc	Phase 2	Pivotal phase 2b trial	2024
BIIB	Lecanemab	Alzheimer's	Regulatory	Regulatory decision from EMA in EU and NMPA in China	1H24
BIIB	Lecanemab subQ	Alzheimer's	Regulatory	subq formulation BLA filing	1Q24
BIIB	Lecanemab	Alzheimer's	Regulatory	IV Maintenance dosing sBLA	1H24
BIIB	Lecanemab	Alzheimer's	Phase 3	DIAN-TU next generation trial read out	TBD
BIIB	Dapirolizumab pego	SLE	Phase 3	Phase 3 PHOENYCS GO readout	2024
BIIB	ATXN2 ASO (BIIB105)	ALS	Phase 1/2	Phase 1/2 Readout	2024
BIIB	UBE3A ASO (BIIB121)	Angelman syndrome	Phase 1	Phase 1 Readout	2024
BIIB	GABAA PAM (BIIB124/SAGE324)	Essential Tremor	Phase 2b	Phase 2b Readout	2024
BMRN	Voxzogo	Idiopathic short stature/ genetic short stature conditions	Phase 3	Initiate Phase 3 clinical trials	2024
BMRN	Roctavian	severe hemophilia A	Approved	Final price in France	Early 2024
BMRN	Roctavian	severe hemophilia A	Approved	Final price in Germany + Italy	Early 2024
BMRN	Roctavian	severe hemophilia A	Approved	J-code going into effect in the US	1-Jan-24
BMRN	BMN 255	primary hyperoxaluria type 1- chronic renal disease	Phase 1	Phase 1 MAD readout	2024
BMRN	BMN 331	Hereditary Angioedema	Phase 1	Phase 1/2 HAERMONY readout	2025
BMRN	BMN 351	DMD	Preclinical	Enabling a global clinical development plan and expects to have a determination of clinical proof of concept in 2025	2025
BMRN	BMN 349	alpha-1 antitrypsin deficiency	Preclinical	Initiate global clinical program in 2024; PoC 2025	2024
BMRN	BMN 293	MYBPC3 hypertrophic cardiomyopathy	Preclinical	Initiate global clinical program in 2024; PoC 2026	2024
BMRN	BMN 365	PKP2 arrhythmogenic cardiomyopathy	Preclinical	Initiate global clinical programs in 2025 with an anticipated clinical PoC by 2027	2025
BMRN	BMN 355	long-QT syndrome	Preclinical	Initiate global clinical programs in 2025 with an anticipated clinical PoC by 2026	2025
GILD	lenacapavir	long acting HIV PrEP	Pivotal	pivotal data from the PURPOSE 1 trial	YE24
GILD	Etrumadenant	colorectal cancer	Phase 2	ARC-9 interim data	1H24
GILD	Magrolimab + azacitidine + venetoclax	AML	Phase 3	1L unfit AML ENHANCE-3	2H24
GILD	Trodelvy	2L NSCLC	Phase 3	Evoke-01	1H24
GILD/ Arcellx	ddCAR (BCMA CAR-T)	MM	Regulatory filing	Regulatory filing	1H25
MRNA	mRNA-3705	MMA	Phase 1/2	Phase 1/2 ongoing	TBD
MRNA	mRNA-1020/-30	flu	Phase 1/2	Phase 1/2 readout	TBD
MRNA	mRNA-1011/-12	flu	Phase 1	Phase 1 initiation	TBD
MRNA	mRNA-1010	flu	Regulatory filing	Regulatory filing	2024
MRNA	mRNA-1083	flu + COVID	Phase 1/2	Approval	2025
MRNA	mRNA-1345	RSV (older adults)	Regulatory Approval	Regulatory decision	March/ April 2024
MRNA	mRNA-3927	PA	Phase 1/2	Select dose and begin dosing in expansion arm	TBD
MRNA	mRNA-3645	GSD1a	Phase 1/2	Preliminary data	TBD
MRNA	mRNA-3705	MMA	Phase 1/2	Launch	By 2028
MRNA	mRNA-1647	CMV	Phase 3	Interim Readout	mid- 2024
MRNA	mRNA-3927	PA	Phase 1/2	Licensed	By 2028

Exhibit 63: Key large-cap biotech catalysts expected in 2024
We've provided a list of company-specific catalysts to pay attention to for 2024

Company	Product	Indication	Phase	Readout	Timing
MRNA/ MRK	mRNA-4157	NSCLC	Phase 3	Phase 3 results	Primary Completion 06/2030
MRNA/ MRK	mRNA-4157	Adjuvant melanoma	Phase 3	Phase 3 results	Primary Completion 10/2029
REGN	Eylea patent litigation	N/A	Other	Update on patent litigation outcome and LOE	2H24
REGN	odronextamab	r/r DLBCL	Regulatory	accelerated approval in r/r DLBCL	1H24
REGN	Dupixent	COPD	Regulatory	accelerated approval for label expansion into COPD	1H24
REGN	Linvoseltamab (BCMAxCD3)	r/r MM	Regulatory	accelerated approval in r/r MM	1H24
VRTX	exa-cel	TDT	Regulatory decision	PDUFA March 30th 2024	3/30/2024
VRTX	VX-548	Acute pain	Phase 3	Ph3 complete 1Q24	1Q24
VRTX	vanzacaftor	CF	Phase 3	Phase 3 results early 2024	Early 2024
VRTX	VX-548	Neuropathic pain	Phase 2	Phase 2 LSR results	Primary completion 04/2025
VRTX	VX-548	Neuropathic pain	Phase 2	End of phase 2 meeting with FDA on DPN	2024
VRTX	VX-880	Type 1 diabetes	Phase 1/2	updated clinical data	2024
VRTX	VX-264 (cell + device)	Type 1 diabetes	Phase 1/2	Begin enrollment and dosing	Soon
VRTX	VX-634/ VX-668	AATD	Phase 1	Healthy volunteer results	TBD
VRTX	VX-522 (mRNA)	CF	Phase 1	MAD portion of study by 2023e	2024

Source: Company reports; BofA Global Research

BofA GLOBAL RESEARCH

Abbreviations:
1L: first line therapy
2L: second line therapy
AACR: American Association for Cancer Research
AAO: American Academy of Ophthalmology
AATD: alpha-1 antitrypsin deficiency
Abeta: amyloid beta
ACIP: Advisory Committee on Immunization Practices
ADC: antibody drug conjugate
AHA: American Heart Association
AKMD: APOL1-Mediated Kidney disease
ALS: amyotrophic lateral sclerosis
AML: acute myeloid leukemia
AOM: anti-obesity medication
APOL1: apolipoprotein L1
ARDS: acute respiratory syndrome
ARIA: Amyloid-related imaging abnormalities
ASCO: American Society of Clinical Oncology
ASCVD: atherosclerotic cardiovascular disease
ASH: American Society of Hematology
ATC: authorized treatment centers
ATS: American Thoracic Society
B7H3, CDH6, Claudin 18.2, HER3, TROP2: common targets for ADCs
BCL2: B-cell leukemia/lymphoma 2
BCMA: B-cell maturation antigen
BD: business development
BLA: Biologics License Application
BMI: Body mass index
CAGR: compound annual growth rate
CAR-T: chimeric antigen receptor T cell
Cas12b: CRISPR-associated endonuclease 12b
CBER: Center for Biologics Evaluation and Research
CCA: Cholangiocarcinoma
CD: crohn's disease
CD20: B-cell marker
CD34+: cluster of differentiation 34+
CD47: cluster of differentiation 47
CD73: cluster of differentiation 73
CDER: Center for Drug Evaluation and Research
CDR-SB: Clinical Dementia Rating scale Sum of Boxes
CF: cystic fibrosis
Cis: cisplatin
CLL: chronic lymphocytic lymphoma
CMC: chemistry, manufacturing, and controls
CMS: Centers for Medicare & Medicaid Services
CMV: Cytomegalovirus
CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
CR: complete response
CRC: colorectal cancer
CRISPR/Cas9: gene-editing technology
CRL: complete response letter
CROI: Conference on Retroviruses and Opportunistic Viruses
CRPC: Castration-resistant prostate cancer
CRS: cytokine release syndrome
CTAD: Clinical Trials on Alzheimer's Disease conference
CTLA-4: cytotoxic T-lymphocyte antigen-4
CV: cardiovascular
DB: Demodex Blepharitis
DL: dose level
DLBCL: diffuse large B-cell lymphoma

DMD: Duchenne Muscular Dystrophy
DPN: diabetic peripheral neuropathy
EBMT: European Society for Blood and Marrow Transplantation
EGFR: epidermal growth factor receptor
EMA: European Medicines Agency
ESMO: European Society for Medical Oncology
EU: European Union
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
FGFR2/ EGFR: genes
FL: follicular lymphoma
FTC: Federal trade commission
GCA: giant cell arteritis
GCIS: global industry classification standard
Gene names: FGF21
GGG: GLP-1, GIP, and glucagon
GIP: Glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide 1
GSK: GlaxoSmithKline
H&N: head and neck
HBV: hepatitis B virus
HC: healthcare
HCC: hepatocellular carcinoma
HER2: human epidermal growth factor receptor 2
HFpEF: heart failure with preserved ejection fraction
hHSPCs: hematopoietic stem and progenitor cell
HIV: human immunodeficiency virus
HNSCC: head and neck squamous cell carcinoma
HR: hormone receptor
I&I: inflammation and immunology
iADRS: integrated Alzheimer's Disease Rating Scale
IBD: inflammatory bowel disease
IL-2: Interleukin-2
IL-23: Interleukin-23
IND: Investigational new drug
INT: individualized neoantigen therapy
IO: immuno-oncology
IPO: initial public offering
IRA: inflation reduction act
IRAK4: interleukin-1 receptor-associated kinase 4
IRAKiMID: interleukin 1 receptor-associated kinase and immune-mediated inflammatory diseases
IV: intravenous
JAK: janus kinase inhibitor
KOLs: key opinion leaders
KOR: Kappa opioid receptor
KRAS G12C: kirsten rat sarcoma virus glycine-to-cysteine substitution at codon
La/m UC: locally advanced or metastatic urothelial carcinoma
LAG3: lymphocyte-activation protein 3
LAI: long-acting injjectable
LOE: loss of exclusivity
Long QT syndrome: a type of conduction disorder
LPA1: Lysophosphatidic acid receptor 1
LTM: last twelve months
M&A: mergers and acquisitions
M4: muscarinic acetylcholine receptor 4
Mavri: mavrilimumab
MDM2: murine double minute 2
MDS: myelodysplastic syndrome
MET: mesenchymal epithelial transition factor receptor
MIBC: muscle invasive bladder cancer

MM: multiple myeloma
MOA: mechanism of action
mRNA: messenger ribonucleic acid
MS: multiple sclerosis
MSS CRC: Microsatellite stability colorectal cancer
mUC: metastatic urothelial carcinoma
MUC16: mucin 16
MYBPC3/ PKP2: genes
NASH: nonalcoholic steatohepatitis
NCD: national coverage determination
NDA: new drug application
NHL: non-Hodgkin's lymphoma
NMIBC: non muscle invasive bladder cancer
NPV: net present value
NR4A3: nuclear receptor subfamily 4 group A member 3
NSCLC: non-small cell lung cancer
oHCM: obstructive hypertrophic cardiomyopathy
Oncology
OpEx: operating expenses
Oppty: opportunity
ORR: objective response rate
ORR: overall response rate
OS: overall survival
PAH: pulmonary arterial hypertension
PARP: poly(ADP-ribose) polymerase
PCV: personalized cancer vaccine
PD-1: Programmed cell death protein 1
PDUFA: The Prescription Drug User Fee Act
PK: pharmacokinetic
PN: prurigo nodularis
POC: proof of concept
POS: probability of success
PPD: postpartum depression
PrEP: pre-exposure prophylaxis
PSMA: prostate-specific membrane antigen
r/r: relapsed and refractory
RA: Rheumatoid arthritis
RCC: renal cell carcinoma
REMS: Risk Evaluation and Mitigation Strategy
ROR1: receptor tyrosine kinase like orphan receptor 1
ROW: rest of world
RP: recurrent pericarditis
RP: Royalty Pharma
RP2D: recommended phase 2 dose
RSV: respiratory syncytial virus
SC: subcutaneous
SCCHN: squamous cell carcinoma of the head and neck
SCD: Sickle cell disease
SCLC: small cell lung cancer
SHTG: severe hypertriglyceridemia
SLE: systemic lupus erythematosus
SMA: spinal muscular atrophy
SSRI: Selective serotonin reuptake inhibitors
STAT3: signal transducer and activator of transcription 3
T1D: Type-1 diabetes
T2D: type 2 diabetes
TDT: Transfusion-dependent beta-thalassemia
TGFBR2: transforming growth factor-beta receptor type 2'
TIGIT: T-cell immunoreceptor with Ig and ITIM domains
TIL: tumor infiltrating lymphocyte
TKI: tyrosine kinase inhibitor

TNBC: triple-negative breast cancer
TNF: tumor necrosis factor
TYK2: tyrosine kinase 2
UC: ulcerative colitis
WACC: weighted average cost of capital
WW: worldwide

Investment Rationale

Bristol-Myers Squibb
Our Neutral rating is driven by the uncertainty on long-term growth profile of the company given LOE headwinds despite recent acquisitions. That said, BMY has multiple new launches (recent/ upcoming) which could potentially re-rate the stock if the company can execute the launch successfully.

Kymera Therapeutics
We like Kymera's story, as we see a positive risk/reward moving into this year's major data readout, and see an opportunity for increased momentum over the next few months. We'd argue that valuation from here will be driven almost entirely by increased probabilities of success for Kymera's lead programs (IRAK4 and STAT3).

Price objective basis & risk

89bio, Inc (ETNB)
Our DCF-based derived PO of $25 for ETNB includes $19/share for pegozafermin in NASH and $3/share for pegozafermin in SHTG. The remaining value in our PO comes from cash. We use a 15% WACC in NASH and SHTG and assume no terminal value for ETNB.

Upside risks to our price objective are 1) additional positive clinical results in NASH showing potential dosing superiority, 2) positive clinical data in SHTG showing differentiation against standard of care, and 3) higher than expected prevalence/diagnosis rate in NASH/SHTG leading to high market penetration.

Downside risks are 1) failure in phase 2b study in NASH, 2) subpar efficacy/lack of dosing advantage of pegozafermin in NASH compared to other FGF21 analogs, 3) low penetration/poor uptake in the NASH/SHTG market for pegozafermin and 4) failure to show clinical benefits in SHTG.

AbbVie (ABBV)
Our $160 price objective (PO) is based on a 50/50 blended valuation of our DCF and 2024 non-GAAP EPS estimate P/E multiple of 12x (giving a value of $132). Our 12x P/E multiple lags peers (18.0x) due to concentration risk of the company's assets and LOE concerns to drive significant growth in the future. We assume a 7% WACC and a -1% terminal growth in our estimates to arrive at our $188 DCF valuation.

Downside risks are underachievement of key growth drivers, clinical pipeline failure(s), and reduced cash flow generation to pay down debt or dividend.

Amgen Inc. (AMGN)
Our PO for AMGN is $290 per share. We value AMGN using a sum of the parts NPV analysis of key marketed drugs ($247/sh) and pipeline and others ($122/sh), which

assumes a range of weighted average cost of capital (WACC) from 5% and terminal growth rate ranging from -5% to -30% depending on the product lifecycle. Our PO also reflects -$79/sh in net debt.

Upside risks to our price objective are 1) less than-expected base business erosion2) stronger-than-expected sales of Lumakras, Tezspire, Tepezza, and 3) competitor clinical trial failures

Downside risks to our price objective are 1) faster-than-expected revenue erosion from legacy brands, 2) slower-than-expected growth of new drug launches, and 3) clinical trial failures.

Amylyx Pharmaceuticals (AMLX)
Our $42 PO is based on probability-adjusted NPV analysis of AMX0035 in ALS ($37/sh) and net cash ($6/sh). We model AMX0035 revenues through 2035 in key markets including US, Canada, and Europe, and apply a 15% WACC and -35% terminal growth rate.

Upside Risks to our PO
1) Positive confirmatory phase 3 PHOENIX trial readout in 2024 that drives strong market uptake, especially in OUS markets, 2) better than expected reimbursement and market uptake.

Downside Risks to our PO
1) failure to receive approval in EU, 2) commercial pushback from payers and providers, 3) failure of confirmatory phase 3 PHOENIX trial, resulting in pushback from payers and providers and drug could be withdrawn from the market.

Biogen Inc. (BIIB)
Our $290 price objective is based on a sum-of-the parts net present value (NPV) analysis and a discount rate of 8%. We value the MS franchise at $74/share, Spinraza at $36/share, Roche collaboration/royalty at $64/share, biosimilars at $7/share, Alzheimer's at $87/share, zuranolone at $7/share, Skyclarys at $42/share, the pipeline at $5/share, and net cash at -$33/share.

Upside risks to our PO are 1) less erosion of Tecfidera, Avonex, Plegridy, and Tysabri than anticipated, 2) Vumerity meaningfully capturing market share, 3) durability of Spinraza, 4) rapid uptake of lecanemab, and 5) success of a number of pipeline programs

Downside risks are 1) greater-than-expected moderation of MS sales (Tecfidera, Avonex, Plegridy, and Tysabri) due to increased competition/ generics, 2) rapid erosion of Spinraza's market share in SMA, 3) limited success of the R&D pipeline, with many products failing to advance or approved with narrow indications for smaller patient populations, and 4) limited uptake of lecanemab.

BioMarin (BMRN)
Our valuation approach for BMRN shares employs a discounted cash flow analysis of approved and pipeline products reflected in our $170 price objective. We value BioMarin shares using a sum-of-the-parts net present value (NPV) analysis of approved assets, which assumes a weighted average cost of capital (WACC) of 4.5% and terminal growth rate of -5.5%. Under our assumptions, our NPV analysis suggests a legacy product value of $55/share, Roctavian and Voxzogo of $95/share, early stage pipeline of $11/share and cash value of $9/share.

Risks to our price objective are 1) faster-than-expected revenue runoff from Kuvan, 2) competition from other orphan drug developers, 3) slower-than-expected growth of new drug launches, and 4) clinical trial failures.

Bristol-Myers Squibb (BMY)
Our $60 price objective (PO) is based on a 50/50 blended average of our risk-adjusted discounted cash flow (DCF) and P/E multiple applied to 2024E EPS. Our DCF assumes 7% WACC and -4% terminal growth rate, and we assume an approximate 8x 2024 P/E multiple given an impending patent cliff and risks associated with later-stage pipeline.

Risks to our PO are 1) uninspiring readouts from late-stage trials in key I/O indications, 2) more rapid deceleration of Revlimid erosion than expected, 3) negative outcomes from the company's later-stage pipeline assets in development, 4) pressures from headline risks facing the sector (including drug pricing reform), and 5) negative patent rulings.

Caribou (CRBU)
Our $20/share price objective is based on a probability adjusted NPV of CB-010 ($5/sh), CB-011 ($4/sh), CB-012 ($3/sh), CB-020 ($3/sh), early pipeline and partnerships ($1/sh), and cash ($4/sh). We apply a WACC of 11-13% and 3% terminal growth rate, which is comparable to our valuation methodology for other biotech companies of similar size and stage of clinical development.

Downside risks: 1) initial clinical data for pipeline programs fails to demonstrate a meaningful benefit in patients, 2) pipeline therapies fail to differentiate from similar competing products, 3) regulatory/reimbursement environment weighs on commercial economics, 4) patent litigation invalidates or otherwise undermines the IP portfolio, 5) funding is insufficient to move forward pipeline aspirations or manufacturing buildout.

CRISPR Therapeutics (CRSP)
Our $100 price objective for CRISPR Therapeutics is based on a probability adjusted (35-80%) net present value (NPV) sum-of-the-parts analysis of its four primary programs under development. We use a weighted-average cost of capital (WACC) of 12%, similar to other early-stage companies in our coverage universe, and a 2% terminal growth rate given the long patent life (2033 at earliest) and difficulty of replication. Given these assumptions, our $100 PO includes $44/share for CTX001, $3/share for CTX112, $2/share for CTX121, $4/share for CTX131, $22/share in net cash, and $25/share for the technology platform.

Downside risks: 1) failure of early clinical trials, 2) dangerous safety signals, 3) superior competitor data, and 4) soft market uptake.

CureVac (CVAC)
Our $6.40/share PO is based on a probability-adjusted net present value (NPV) of CureVac's pipeline, including its oncology program and its other prophylactic vaccines. We apply a 10% weighted-average cost of capital (WACC) and a terminal value ranging from -15% to -5% depending on the program (we project revenues out through 2035), in line with other biotech companies of similar size and stage of clinical development. We also include approximately $2/share from CureVac's current cash position.

Upside risks are 1) faster-than-expected clinical development, 2) competitor failures, 3) better than expected clinical data.

Downside risks are 1) clinical risk to early stage programs, 2) regulatory risk from newer mechanisms, 3) competition to key assets.

Eli Lilly and Company (LLY)
Our $700 price objective is based on a probability-adjusted net present value (NPV) analysis of franchise verticals including Endocrinology ($393/share), Oncology ($127/share), Cardiovascular ($4/share), Neuroscience ($12/share), Immunology ($28/share), other pharmaceutical products and early pipeline assets ($150/share), as

well as approximately -$15/share in net cash. We use a WACC ranging from 5% for approved products to 9% for pipeline products, depending on the stage of development. We apply terminal values ranging from -12% (cardiology) to 1% (endocrinology) based on projected sales decline following loss of exclusivity within each business vertical.

Risks to our price objective are 1) better-than-expected launches of competing products, 2) emerging clinical data for pipeline assets that does not confirm prior observations, 3) failure to effectively commercialize approved products, 4) potential drug pricing system restructuring in the US.

Gilead Sciences Inc. (GILD)
Our $95 price objective is based on a sum-of-the parts net present value (NPV) analysis. We forecast sales of key franchises or products to 2030 using a weighted average cost of capital (WACC) of 8%, and include a terminal value where appropriate. Under these assumptions, we value the HIV franchise at $80/share, HCV and HDV at $7/share, the Kite platform at $8/share, remdesivir at $2/share, Trodelvy at $9/share, with the pipeline at $5/share and net cash at -$15/share.

Upside risks: 1) stronger-than-expected sales of Biktarvy in HIV and faster uptake of Descovy in PrEP, 2) greater durability of HCV revenues, 3) rapid uptake of Kite, 4) and success of the oncology pipeline may lead investors to assign further value to these programs.

Downside risks: 1) moderating sales of Biktarvy, Genvoya, Odefsey, and Descovy due to competition, which may include long-acting injectable formulations, 2) greater than expected erosion of HCV revenues, 3) limited upside from Gilead's CAR-Ts, 4) the oncology pipeline may have limited clinical success or be meaningfully delayed.

Janux Therapeutics (JANX)
Our $21 PO is based on a probability-adjusted NPV Janux's pipeline, including its PSMA-TRACTr program for prostate cancer ($8/sh), its EGFR-TRACTr program for colorectal cancer ($5/sh), and its TROP2-TRACTr program for triple-negative breast cancer ($2/sh). We forecast revenue through 2038 and assume a -20% terminal growth rate. We apply a 17-18% WACC and 15%-25% PoS for each program based on the early stage of development. Additional indications for EGFR-TRACTr and TROP2-TRACTr, as well as value for Janux's TRACIr platform are included in a pipeline value ($1/sh), and the remaining value from net cash. Downside risks are: 1) failure of clinical trials, 2) limited commercial uptake, 3) strengthening competitive space.

Downside risks are: 1) failure of clinical trials, 2) limited commercial uptake, 3) strengthening competitive space.

Johnson & Johnson (JNJ)
Our price objective of $180/share is based on a sum of the parts (SOTP) of roughly 18x MedTech multiple, and 14x pharma '24 multiple, slightly below peers given looming loss of exclusivity (LOE) and talc uncertainty, yielding $57/share, and $123/share, respectively.

The downside risks to our PO are slower growth in MedTech due to competitive pressure and faster-than-expected erosion from biosimilars to the pharma business.

Upside risks to our PO are better-than-expected launch of new products, better-than-expected clinical data for the pharma pipeline, quick resolution of talc litigation, and constructive M&A.

Kiniksa Pharmaceuticals, Ltd. (KNSA)

We use a sum of the parts NPV model to value Kiniksa shares based on our risk adjusted revenue forecasts and estimated margin assumptions. Our $28 price objective is based on a sum-of-the parts NPV analysis, forecasting sales of rilonacept out to 2030 using a WACC of 8%, respectively and a terminal value of -7.5%. Under our assumptions, we value rilonacept at $25/share, the pipeline at $0/share and net cash of approximately $3/share.

Upside risks to our PO are: 1) stronger than expected phase 3/ phase 2 POC data, 2) upside to rilonacept launch expectations, and 3) rapid progression of KPL-404 and mavrilimumab development.

Downside risks to our PO are: 1) clinical trial failures, 2) greater than expected competitive threats, 3) delays in product approvals or pipeline developments, 4) unanticipated safety concerns, and 5) financial risks due to available cash.

Kymera Therapeutics (KYMR)
We use a sum of the parts NPV model to value Kymera shares based on our risk-adjusted revenue forecasts and estimated margin assumptions. Our $30 price objective gives credit to the company's two lead programs, KT-474 and STAT3, through 2039 and uses an 15% WACC for both programs.

Downside risks to our PO are: 1) unanticipated safety concerns in initial clinical studies, 2) clinical trial failures / limited efficacy results given preclinical nature of current data, 3) greater than expected competitive threats, 4) delays in pipeline development timelines, and 5) financial risks due to cash availability.

Upside risks to our PO are: 1) positive initial data sooner than expected, 2) additional pipeline partnerships that help de-risk the TPD mechanism, 3) more rapid advancement through the clinic and thus earlier commercial launch timelines, and 4) positive clinical data from other TPD companies that help de-risk the technology.

Lyell Immunopharma (LYEL)
Our $9 PO is based on a probability-adjusted NPV of Lyell's pipeline, including LYL797 in NSCLC and TNBC, LYL845 in melanoma, head and neck cancer, and colorectal cancer, and earlier stage pipeline assets. We apply a 13-16% WACC in-line with similar preclinical stage biotechs (we project revenues through 2035). We also include $3/share from Lyell's cash position.

Downside risks to our PO are 1) clinical trial failures, 2) better-than-expected data from competitors, 3) dilution from cash raises

Merck & Co. (MRK)
Our $130 price objective (PO) is based on the intrinsic value of Merck standalone. We use a 50/50 blended average of our P/E multiple applied to 2024E EPS (we think the current 17x vs.18x peer average makes sense to reflect continued strength of Merck's core growth franchises but broader Keytruda concentration risk concerns) and risk-adjusted DCF (7% WACC and -2% terminal growth rate).

Risks to our PO are 1) impressive competitor readouts results in key immuno-oncology (I/O) indications, 2) more rapid declines across the diabetes franchise than expected, 3) negative outcomes from the company's later-stage assets in ongoing development, and 4) pressures from headline risks facing the sector (including drug pricing reform).

Moderna (MRNA)
Our PO of $120 is based on a probability-adjusted NPV of six different parts including prophylactic vaccines ($91/share), systemic secreted cell surface therapeutics ($1/share), cancer vaccines ($4/share), intratumoral immune-oncology ($2/share), cardiovascular

diseases ($0/share) and systemic intracellular therapeutics ($1 share), and net cash ($22/share). We estimate sales of 46 pipeline programs that are slated to move forward with probability of success ranging from 6% to 95%. We use a WACC of 10% and terminal growth rate of -30%.

Upside risks to our PO are: 1) faster than expected pipeline development, 2) cleaner than expected safety findings, 3) accelerated product approvals, 4) stronger than expected launches, 5) lower competition, 6) moderating cash burn, and 7) potential upside from coronavirus vaccine program.

Downside risks to our PO are: 1) lower than expected revenues from the COVID-19 program, 2) unexpected safety findings, 3) slower than expected pipeline development/approvals, 4) more intense competition, and 5) accelerating cash burn.

Neumora Therapeutics (NMRA)
Our 12-month price objective of $20 is based on our NPV analysis on key products, including navacaprant for MDD, bipolar depression, and NMRA-266 for schizophrenia. We assign a valuation of $14/sh to navacaprant in MDD, $1/sh to navacaprant in bipolar depression, and $2/sh to NMRA-266 in schizophrenia, with the remaining $2/sh coming from net cash. We model sales through patent exclusivity with zero terminal value and apply a 14% WACC.

Upside risks to our PO:
1) Positive navacaprant MDD readouts in 2H24/1H25, 2) readthrough from competitor J&J's aticaprant's positive phase 3 adjunctive MDD data in 2H24, 3) readthrough from competitor Cerevel's emraclidine phase 2 EMPOWER data in 2H24.

Downside risks to our PO:
1) Failure of MDD trial readout, 2) failure of competitors' data in MDD, 3) weak market uptake for Karuna's schizophrenia drug and Axsome's MDD drug could dampen investor enthusiasm for the neuropsychiatric markets.

Pfizer (PFE)
Our $35/share for Pfizer is based on a 50/50 blended average of our discounted cash flow (DCF) analysis and P/E multiple based on the large cap global therapeutics group. For our DCF, we use a weighted-average cost of capital (WACC) of 7% and 2% terminal growth for an intrinsic value of $47/share. Our P/E analysis assumes a 10x multiple of our 2024 EPS estimate, which yields a $22 intrinsic value.

Downside risks: 1) sales downside, 2) inability for pipeline to overcome patent loss of exclusivities (LOEs) after 2025, 3) M&A transactions that are perceived to be value destructive.

Regeneron Pharmaceuticals Inc. (REGN)
Our $700 price objective is based on a probability-adjusted net present value (NPV) analysis of Eylea, including outside of US (OUS) revenues from the Bayer collaboration ($164/share), Sanofi collaboration revenue including Dupixent and other product revenues ($329/share), Libtayo ($56/share), early pipeline assets ($60/share), and the rest from net cash. We use a weighted-average cost of capital (WACC) ranging from 7% for approved products to 10% for pipeline products and terminal growth ranging from -3 to 3%. Upside risks to our price objective are 1) better-than-expected Eylea growth trajectory, 2) a larger contribution of Dupixent to Regeneron's topline from commercial uptake in new indications, and 3) better-than-expected economics realized by Regeneron from joint ventures. Downside risks to our price objective are 1) slower-than-expected growth from product sales, particularly Eylea and Dupixent, 2) failure to obtain approval for additional indications for Dupixent, and 3) pipeline setbacks.

Royalty Pharma (RPRX)
Our $40/share price objective is based on a probability-adjusted SOTP NPV analysis which includes current growth products ($34/sh, 80% of our valuation), and projected revenues from future investments ($11/sh, 31%). We project out revenues through 2038, apply a WACC of 5% (mature products) to 8% (future growth products), and use terminal growth rates ranging from -5% (current growth products) to 5% (future growth products), in-line with other mature biopharma companies. We calculate net cash as -$5/sh (-11% of our valuation).

Downside risks: 1) current portfolio royalties do not reach current assumed levels, 2) new investments fail to replicate historical returns, 3) new corporate structure and shareholder base adversely impacts historically low tax rate, 4) competition in the royalty investing space makes it harder to attain new value accretive investments, 5) patent/royalty expiries are not replaced by new royalty streams.

Sana Biotechnology (SANA)
Our $10 PO is based on a probability-adjusted NPV of Sana's pipeline (12% likelihood of success), including its in vivo and ex vivo platform programs. We apply a 15% WACC and a terminal growth of -30% (we project revenues out through 2035), in-line with other biotech companies of similar size and stage of clinical development. We also include approximately $2/share from Sana's current cash position.

Downside risks to our PO are: 1) clinical trial failures, 2) better than expected data from competitors, 3) dilution from cash raises.

Turnstone Biologics (TSBX)
Our 12-month PO of $15 is based on a probability adjusted SOTP NPV of TIDAL-01 in melanoma (42% of our valuation) and other solid tumors, primarily breast / CRC / uveal melanoma (3% of our valuation). We assign a valuation of $1/share valuation to TIDAL-02 (3% of our valuation), given its stage of development. We apply a midpoint WACC of 15% (13-17%) and -10% terminal growth rate, which is comparable to our valuation methodology for other biotech companies of similar size and stage of clinical development. The remaining $3/sh comes from net cash.

Upside risks to our PO: 1) Lifileucel enjoys a broad label following approval, supporting robust coverage and uptake with positive read-through to the TIL space, 2) TIDAL-01 phase 1 trials enroll faster than expected and data readout comes prior to mid-2024, 3) breakthrough in TIDAL-02 or other pipeline programs, 4) business development contributes non-dilutive funding, 5) improvements in manufacturing bring down costs sooner, and 6) clinical data from the phase 1 TIDAL-01 trials are better than expected.

Downside risks to our PO: 1) Failure of lifileucel to receive accelerated approval in advanced refractory melanoma, 2) delays in TIDAL-01 clinical development, 3) cash balance is insufficient to fund TIDAL-01 clinical development through initial data mid-2024, 4) manufacturing and/or supply chain issues prevent production of selected TIL products, and 5) phase 1 TIDAL-01 clinical trials do not support continued development.

Vertex Pharmaceuticals Inc. (VRTX)
Our 12-month price objective for Vertex of $450/share is based on our net present value (NPV) analysis. We forecast sales for each of the approved products, Kalydeco, Orkambi, Symdeko, and Trikafta through 2030. We assume a weighted-average cost of capital (WACC) of 9%, in line with peer companies of similar size and risk and varying terminal growth rates for each asset based on its characteristics and patent life (-50% to 2%). Given these assumptions, we estimate a value of $4/share for Kalydeco, $2/share for Orkambi, $0/share for Symdeko, $335/share for Trikafta, $31/share for CTX001, $17/share for VX-548, $46/share in net cash, and $15/share for the pipeline.

Risks to our price objective are 1) payer pushback on pricing, 2) difficulty in securing reimbursement agreements, particularly in the EU, 3) clinical trial failures, and 4) new competitors in cystic fibrosis.

Analyst Certification

I, Geoff Meacham, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

Special Disclosures

BofA Securities is currently acting as financial advisor to Bristol-Myers Squibb Co. in connection with its proposed acquisition of RayzeBio, Inc., which was announced on December 26, 2023.

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
BUY				
	89bio, Inc	ETNB	ETNB US	Geoff Meacham
	Acumen Pharma	ABOS	ABOS US	Geoff Meacham
	Agios Pharmaceuticals	AGIO	AGIO US	Greg Harrison, CFA
	Amylyx Pharmaceuticals	AMLX	AMLX US	Geoff Meacham
	BioMarin	BMRN	BMRN US	Geoff Meacham
	BioXcel Therapeutics	BTAI	BTAI US	Greg Harrison, CFA
	BridgeBio Pharma	BBIO	BBIO US	Greg Harrison, CFA
	Caribou	CRBU	CRBU US	Geoff Meacham
	CRISPR Therapeutics	CRSP	CRSP US	Geoff Meacham
	Eli Lilly and Company	LLY	LLY US	Geoff Meacham
	Erasca	ERAS	ERAS US	Alec W. Stranahan
	Esperion	ESPR	ESPR US	Jason Zemansky
	Exscientia	EXAI	EXAI US	Alec W. Stranahan
	Gilead Sciences Inc.	GILD	GILD US	Geoff Meacham
	HUTCHMED	HCM	HCM US	Alec W. Stranahan
	Immatics	IMTX	IMTX US	Alec W. Stranahan
	Insmed Incorporated	INSM	INSM US	Jason Zemansky
	Intellia Therapeutics	NTLA	NTLA US	Greg Harrison, CFA
	Janux Therapeutics	JANX	JANX US	Geoff Meacham
	Keros	KROS	KROS US	Greg Harrison, CFA
	Kiniksa Pharmaceuticals, Ltd.	KNSA	KNSA US	Geoff Meacham
	Krystal Biotech	KRYS	KRYS US	Alec W. Stranahan
	Kura Oncology	KURA	KURA US	Jason Zemansky
	Liquidia Corporation	LQDA	LQDA US	Greg Harrison, CFA
	Lyell Immunopharma	LYEL	LYEL US	Geoff Meacham
	MeiraGTx	MGTX	MGTX US	Alec W. Stranahan
	Merck & Co.	MRK	MRK US	Geoff Meacham
	Mineralys Therapeutics	MLYS	MLYS US	Greg Harrison, CFA
	Neumora Therapeutics	NMRA	NMRA US	Geoff Meacham
	Rani Therapeutics	RANI	RANI US	Geoff Meacham
	Regenxbio, Inc.	RGNX	RGNX US	Alec W. Stranahan
	Rocket Pharmaceuticals, Inc.	RCKT	RCKT US	Greg Harrison, CFA
	Royalty Pharma	RPRX	RPRX US	Geoff Meacham
	Sana Biotechnology	SANA	SANA US	Geoff Meacham
	SpringWorks	SWTX	SWTX US	Alec W. Stranahan
	Syndax Pharmaceuticals	SNDX	SNDX US	Jason Zemansky
	Travere Therapeutics Inc	TVTX	TVTX US	Greg Harrison, CFA
	Turnstone Biologics	TSBX	TSBX US	Geoff Meacham
	Vertex Pharmaceuticals Inc.	VRTX	VRTX US	Geoff Meacham
	Werewolf Therapeutics	HOWL	HOWL US	Jason Zemansky
	Xencor	XNCR	XNCR US	Alec W. Stranahan
NEUTRAL				
	AbbVie	ABBV	ABBV US	Geoff Meacham
	Alector, Inc	ALEC	ALEC US	Greg Harrison, CFA
	Amgen Inc.	AMGN	AMGN US	Geoff Meacham
	Arcus Biosciences	RCUS	RCUS US	Jason Zemansky
	Beam Therapeutics	BEAM	BEAM US	Greg Harrison, CFA
	Biogen Inc.	BIIB	BIIB US	Geoff Meacham
	Bristol-Myers Squibb	BMY	BMY US	Geoff Meacham
	Cytokinetics, Incorporated	CYTK	CYTK US	Jason Zemansky
	Editas Medicine	EDIT	EDIT US	Greg Harrison, CFA
	IGM Biosciences	IGMS	IGMS US	Greg Harrison, CFA
	Johnson & Johnson	JNJ	JNJ US	Geoff Meacham
	Kymera Therapeutics	KYMR	KYMR US	Geoff Meacham
	Moderna	MRNA	MRNA US	Geoff Meacham
	Pfizer	PFE	PFE US	Geoff Meacham
	Recursion Pharmaceuticals, Inc.	RXRX	RXRX US	Alec W. Stranahan
	Revolution Medicines	RVMD	RVMD US	Alec W. Stranahan
	Tyra Biosciences	TYRA	TYRA US	Greg Harrison, CFA
	Vir	VIR	VIR US	Geoff Meacham
	Y-mAbs Therapeutics, Inc	YMAB	YMAB US	Alec W. Stranahan
UNDERPERFORM				
	AlloVir, Inc.	ALVR	ALVR US	Jason Zemansky

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
	CureVac	CVAC	CVAC US	Geoff Meacham
	Day One Biopharmaceuticals	DAWN	DAWN US	Alec W. Stranahan
	LianBio	LIAN	LIAN US	Geoff Meacham
	Novavax	NVAX	NVAX US	Alec W. Stranahan
	Regeneron Pharmaceuticals Inc.	REGN	REGN US	Geoff Meacham
	Reneo Pharmaceuticals	RPHM	RPHM US	Jason Zemansky
	TG Therapeutics	TGTX	TGTX US	Alec W. Stranahan
	United Therapeutics Corporation	UTHR	UTHR US	Greg Harrison, CFA

Disclosures

Important Disclosures

Equity Investment Rating Distribution: Health Care Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	234	60.94%	Buy	115	49.15%
Hold	80	20.83%	Hold	36	45.00%
Sell	70	18.23%	Sell	29	41.43%

Equity Investment Rating Distribution: Global Group (as of 31 Dec 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1895	53.62%	Buy	1083	57.15%
Hold	832	23.54%	Hold	454	54.57%
Sell	807	22.84%	Sell	383	47.46%

[R1] Issuers that were investment banking clients of BofA Securities or one of its affiliates within the past 12 months. For purposes of this Investment Rating Distribution, the coverage universe includes only stocks. A stock rated Neutral is included as a Hold, and a stock rated Underperform is included as a Sell.

FUNDAMENTAL EQUITY OPINION KEY: Opinions include a Volatility Risk Rating, an Investment Rating and an Income Rating. VOLATILITY RISK RATINGS, indicators of potential price fluctuation, are: A - Low, B - Medium and C - High. INVESTMENT RATINGS reflect the analyst's assessment of both a stock's absolute total return potential as well as its attractiveness for investment relative to other stocks within its Coverage Cluster (defined below). Our investment ratings are: 1 - Buy stocks are expected to have a total return of at least 10% and are the most attractive stocks in the coverage cluster; 2 - Neutral stocks are expected to remain flat or increase in value and are less attractive than Buy rated stocks and 3 - Underperform stocks are the least attractive stocks in a coverage cluster. An investment rating of 6 (No Rating) indicates that a stock is no longer trading on the basis of fundamentals. Analysts assign investment ratings considering, among other things, the 0-12 month total return expectation for a stock and the firm's guidelines for ratings dispersions (shown in the table below). The current price objective for a stock should be referenced to better understand the total return expectation at any given time. The price objective reflects the analyst's view of the potential price appreciation (depreciation).

Investment rating	Total return expectation (within 12-month period of date of initial rating)	Ratings dispersion guidelines for coverage cluster[R2]
Buy	≥ 10%	≤ 70%
Neutral	≥ 0%	≤ 30%
Underperform	N/A	≥ 20%

[R2] Ratings dispersions may vary from time to time where BofA Global Research believes it better reflects the investment prospects of stocks in a Coverage Cluster.

INCOME RATINGS, indicators of potential cash dividends, are: 7 - same/higher (dividend considered to be secure), 8 - same/lower (dividend not considered to be secure) and 9 - pays no cash dividend. *Coverage Cluster* is comprised of stocks covered by a single analyst or two or more analysts sharing a common industry, sector, region or other classification(s). A stock's coverage cluster is included in the most recent BofA Global Research report referencing the stock.

Price Charts for the securities referenced in this research report are available on the Price Charts website, or call 1-800-MERRILL to have them mailed.
BofAS or one of its affiliates acts as a market maker for the equity securities recommended in the report: 89bio, Inc, AbbVie, Amgen Inc., Amylyx, Biogen Inc., BioMarin, Bristol-Myers Squibb, Caribou, CRISPR Therapeutics, CureVac, Eli Lilly, Gilead Sciences Inc., Janux, Johnson & Johnson, Kiniksa Pharmaceutic, Kymera Therapeutics, Lyell Immunopharma, Merck & Co., Moderna, Neumora, Pfizer, Regeneron Pharmaceut, Royalty Pharma, Sana Biotechnology, Turnstone, Vertex Pharmaceutica.
BofAS or an affiliate was a manager of a public offering of securities of this issuer within the last 12 months: 89bio, Inc, Amgen Inc., Bristol-Myers Squibb, Caribou, Gilead Sciences Inc., Janux, Merck & Co., Neumora Therapeutics, Turnstone Biologics.
The issuer is or was, within the last 12 months, an investment banking client of BofAS and/or one or more of its affiliates: 89bio, Inc, Abbvie Inc, Amgen Inc., Amylyx Pharmaceutica, Biogen Inc., BioMarin, Bristol-Myers Squibb, Caribou, Eli Lilly, Gilead Sciences Inc., Janux, Johnson & Johnson, Merck & Co., Neumora Therapeutics, Pfizer, Regeneron Pharmaceut, Royalty Pharma, Turnstone Biologics, Vertex Pharmaceutica.
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The issuer is or was, within the last 12 months, a non-securities business client of BofAS and/or one or more of its affiliates: 89bio, Inc, Abbvie Inc, Amgen Inc., Amylyx Pharmaceutica, Biogen Inc., BioMarin, Bristol-Myers Squibb, Caribou, CRISPR Therapeutics, Eli Lilly, Gilead Sciences Inc., Janux, Johnson & Johnson, Kymera Therapeutics, Merck & Co., Moderna, Pfizer, Regeneron Pharmaceut, Royalty Pharma, Vertex Pharmaceutica.
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