MORNINGSTAR®

Healthcare Observer

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Annual Drug Pipeline Report: Moats and ROICs Look Stable; Innovation Supports Growth With Minimal Coronavirus Headwinds

Most Big Pharma and Big Biotech stocks in our coverage support wide moats as a result of their ability to generate new drugs to replace mature ones losing patent protection. We project 4.7% annual average sales growth through 2024 (similar to consensus) for the 18 moatiest pharma and biotech names in our coverage, as innovation more than counters generic/biosimilar and branded competitive threats. Overlaying our growth analysis with valuation, we see underappreciated areas: Roche's Tecentriq in several cancer niches; Bristol's steady position in immuno-oncology and massive pipeline and cash flow support from Celgene; Merck's oncology portfolio and vaccine and animal health cash flows; Pfizer's new immunology drugs and strong vaccine positioning.

In the COVID-19 pipeline, key drivers include Gilead's antiviral remdesivir, multiple vaccines, and targeted antibodies. While these products support our moat ratings indirectly (greater appreciation of innovation and reduced risk of severe price cuts), we don't see significant sales from COVID-19 products due to their expected nonprofit status (only remdesivir and REGN-COV2 are in our models).

Large-Cap Drug Stocks With Strong Pipeline Potential and Attractive Valuation

		Top-Line Growth, 2019-2024E		
Firm (Ticker)	P/FV	Morningstar	Consensus	Summary
Bristol (BMY)	0.89	11.9%	13.6%	The Celgene acquisition brought strong Revlimid cash flows and a late-stage pipeline launching in 2020-21 to counter Opdivo's lung cancer disappointments and Bristol's thinner pipeline.
Merck (MRK)	0.80	5.0%	4.0%	Merck's oncology portfolio (led by Keytruda) and diversification with strong vaccine and animal health units support strong long-term growth potential despite new competition.
Pfizer (PFE)	0.81	2.5%	1.0%	Pfizer's immunology pipeline led by atopic dermatitis drug abrocitinib along with an established and innovative vaccine platform supports steady growth.
Roche (RHHBY)	0.81	4.8%	3.6%	Tecentriq's potential in lung, breast, and liver cancers and adjuvant indications support our above-consensus sales projections, and oncology and neurology pipelines look full.

Source: Morningstar, company reports. Price data as of July 6, 2020.
Note: While our Bristol 2024 sales projections are below consensus, a major driver is our below consensus expectations for Revlimid in 2024 due to generic pressure, but we are more bullish on pipeline drugs with longer periods of future exclusivity.

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Inline Products and Pipelines Support 5% Five-Year Organic Growth

- The large U.S. and European pharma and biotech firms (see Exhibit 1 for specific firms) are poised to see average annual top-line growth of 5% through 2024 (in line with consensus), and R&D productivity (as measured by ROICs) looks largely stable over the next several years (see Page 7).
- The COVID-19 pandemic has only minor impact on monetizing innovative drugs, causing a less-than 2% aggregate impact on our valuations in this space, and we expect the upcoming payer mix shift to the lower-priced Medicaid market (due to COVID-related job losses) to have no more than a 1.5% impact on sales (see Page 9). In the COVID-19 pipeline, we don't model vaccine sales directly as we assume them to be not-for-profit at most Big Pharma firms, but we do explicitly model Gilead's antiviral remdesivir ($3 billion peak) and Regeneron's antibody cocktail REGN-COV2 ($2 billion peak).
- On U.S. drug policy, we think Joe Biden's status as the presumptive Democratic nominee for president takes significant reform off the table, despite the recommendation of more-aggressive reforms from the Biden-Sanders unity task force. We estimate a 5% aggregate hit to U.S.-branded drug sales from more moderate reforms, such as Medicare inflation price caps and Part D redesign, which we still assume have a less-than 50% probability of passing over the next few years and would cause only minor pressure on returns.
- Following Bristol/Celgene and AbbVie/Allergan deals, we still see logic in several larger tie-ups, although most firms are likely to focus on SMID-cap deals to bolster competitive positioning in key therapeutic areas by gaining access to innovative drugs (see M&A takeover grid on Page 19).
- Amgen and Bristol stand to see several potentially key launches through 2021, and we think there could be bigger valuation moves, based on upcoming data in immuno-oncology (adjuvant indications) and blood cancer (BCMA bispecifics versus cell therapies). (See catalysts on Page 20.)

Industry 6% Undervalued in Aggregate; We Highlight Roche, Bristol, Merck, and Pfizer

- The market underappreciates Roche's strong position in immuno-oncology. We expect Tecentriq's approval in a range of cancers including 1L NSCLC, SCLC, TNBC, and HCC and upcoming data in ovarian cancer and adjuvant indications to drive 2024 sales of $11.3 billion ($6.4 billion consensus). (See company overview on Page 143.)
- Our above-consensus view of immuno-oncology supports Bristol's Opdivo, and the Celgene acquisition gives access to strong cash flows through 2022, several potential blockbusters launching by 2021, and dozens of early-stage partnerships. (See company overview on Page 67.)
- Merck's Keytruda franchise is poised to continue to dominate in the largest lung cancer market, with multiple growth opportunities in earlier-stage disease and new indications. The firm's vaccine business (led by Gardasil) and animal health divisions also provide attractive growth. (See company overview on Page 106.)
- Pfizer's emerging immunology pipeline should bring several new drugs to the market with competitive profiles, led by abrocitinib in atopic dermatitis. Strong vaccine development in pneumococcal, C. difficile and RSV should support additional growth. (See company overview on Page 128.)

Exhibit 1 Valuation, Growth, and Patent/Pipeline Exposure for Our 18 Big Pharma/Big Biotech Stocks

				Top-Line Growth, 2019-2024E	
Firm (Ticker)	**Moat**	**P/FV**	**Market Cap ($ Bil)**	**Morningstar**	**Consensus**
AbbVie (ABBV)	Narrow	1.02	174	7.1%	9.9%
Amgen (AMGN)	Wide	1.17	151	4.0%	4.7%
AstraZeneca (AZN)	Wide	0.98	138	10.0%	10.7%
Bayer (BAYRY)	Wide	0.73	74	1.7%	2.3%
Biogen (BIIB)	Wide	0.69	44	-0.8%	-0.3%
BioMarin (BMRN)	Narrow	1.07	23	21.5%	18.2%
Bristol (BMY)	Wide	0.89	136	11.9%	13.6%
Eli Lilly (LLY)	Wide	1.08	160	10.0%	6.5%
Gilead (GILD)	Wide	0.9	96	0.4%	1.7%
GlaxoSmithKline (GSK)	Wide	0.91	102	4.2%	3.8%
Johnson & Johnson (JNJ)	Wide	1.01	377	3.6%	3.4%
Merck (MRK)	Wide	0.8	201	5.0%	4.0%
Novartis (NVS)	Wide	0.97	202	2.4%	3.7%
Novo Nordisk (NVO)	Wide	1.06	154	6.5%	7.1%
Pfizer (PFE)	Wide	0.81	192	2.5%	1.0%
Regeneron (REGN)	Narrow	1.33	64	6.3%	7.3%
Roche (RHHBY)	Wide	0.81	300	4.8%	3.6%
Sanofi (SNY)	Wide	0.95	129	3.1%	2.8%
Total				**4.7%**	**4.7%**

Source: Morningstar, Visible Alpha, company reports. Price and market cap data as of July 6, 2020.

Key Definitions Used Throughout Our Analysis

HR: Hazard ratio, used to assess the risk reduction (or increase) for treatment versus a comparator arm. For example, HR=0.70 means a 30% relative risk reduction on the given endpoint.

OS: overall survival (gold standard for oncology trials)

PFS: progression-free survival (acceptable surrogate endpoint in some cancer indications)

CR: complete response (cancer disappearance or remission, often used as a sign of potential survival benefit in cancers with very long survival times, such as certain forms of blood cancer)

ORR: overall response rate (percentage of patients whose cancer shrinks or disappears)

NSCLC: non-small cell lung cancer

SCLC: small cell lung cancer

HCC: hepatocellular carcinoma

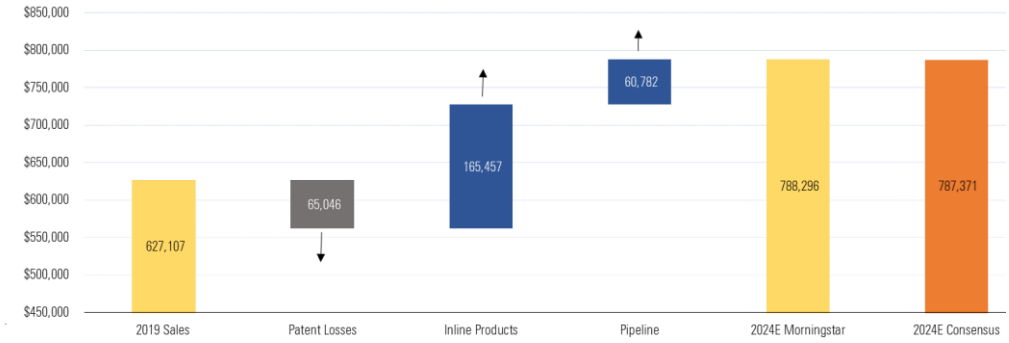
TNBC: triple-negative breast cancer

Five-Year Outlook: Pipelines Offset Patent Losses and Reinforce Moats

Innovation is the central building block for the strong economic moats in the drug and biotechnology industry, supporting drug pricing power and launch trajectories. However, following patent expirations, drug sales fall significantly, making the continuous cycle of new drugs essential to the economic moats in the industry. In looking at the entire large-cap drug and biotech industries, we expect steady innovation to drive 5% annual sales growth over the next five years, similar to consensus expectations.

We divide the outlook for large biotech and pharmaceutical firms into three segments: inline products (approved drugs with generic/biosimilar threats after 2024), products losing exclusivity through 2024, and pipeline drugs (approvals in 2020 and beyond). As shown in Exhibit 2, the bulk of this growth is from inline products that are generally established on the market and at the peak of their growth-generating potential. However, the five-year outlook for pipeline growth is stronger than our last update from January 2019 (representing almost 300 basis points more as a percentage of total 2024 sales).

Exhibit 2 Big Biotech and Big Pharma Growth Outlook Through 2024E ($ Millions)



Source: Morningstar, S&P CapIQ, Drug Analyst, company reports.
Note: Firms included: AbbVie, Amgen, AstraZeneca, Bayer, Biogen, Bristol, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche, and Sanofi.

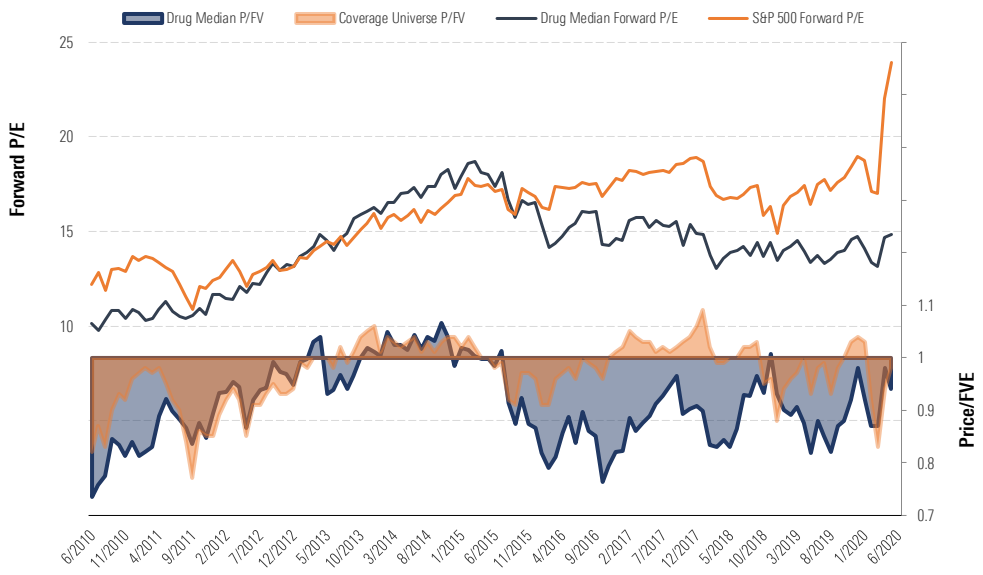
Large-Cap Pharma Can Preserve Moats in Competitive Environments With Focus or Diversification

U.S. payer consolidation and the rising prominence of value-based assessments from the Institute for Clinical and Economic Review have constrained pharma and biotech's ability to price high and pass through annual U.S. price increases, and pending executive branch rules and potential legislation weigh

on valuations. The 18 large-cap pharma and biotech stocks in this report traded at a median price/fair value of 0.94 at the end of May 2020 (a 6% discount to our fair value estimates).

Exhibit 3 shows trends in market and Morningstar valuations of these drug firms compared with the overall market over the past decade. Drug stocks lost their slight multiple premium in mid-2015 as the pricing debate began to swirl, but the spread between drug stock and market multiples narrowed toward the end of 2018, as strong productivity in the drug space and potential for more M&A partly countered overall market volatility. This spread has since widened, partly because of continued threats of U.S. policy reform as we approach a potential Biden administration in 2021 (see Page 12). Extremely expanded multiples for the broader stock universe, due to strong overall stock market performance in the first half of 2020 despite significant near-term headwinds on earnings from the COVID-19 pandemic, which has left earnings at most drug firms relatively unscathed so far, have also widened this spread.

Exhibit 3 Forward Multiples and Morningstar Valuations, Large-Cap Drug Stocks Versus the Market: 2010-20



Source: Morningstar, company reports. Data as of May 31, 2020.

Given the pricing pressure overhang, firms need higher levels of innovation in their pipelines to justify pricing and prevent pharmacy benefit managers from using competition to drag prices down. Slight dosing advantages and minor improvements in efficacy in crowded therapeutic areas will not support the innovation needed for pricing power, as was the case in the 1990s and early 2000s. In areas like respiratory disease (asthma) and diabetes (insulin), next-generation drugs have lacked the differentiation to support the price increases and deepen competitive advantages.

We think large-cap drug companies are adapting to the changing payer landscape and preserving their narrow and wide economic moats, as the majority of pipeline drugs are focused in critical care areas and

represent significant advancements over current treatment options. Regulatory groups are increasingly willing to approve such drugs on limited phase 2 data, and drug companies are pushing drug development speeds to shorten the pathways to increasingly competitive marketplaces.

More novel drugs can mean more development risk, but most large-cap drug firms are in a position to preserve their competitive advantages. We see two different strategies: increase the diversification of drug development by bringing in divisions such as animal health, consumer health, and vaccines that tend to be more stable; increase investment focus on innovation toward areas with strong pricing power, particularly in therapeutic areas that are a core focus of expertise for a given firm. AbbVie diversified into aesthetics with its acquisition of Allergan, while Bristol solidified its oncology and immunology focus with its acquisition of Celgene.

From a moat perspective, diversification is important either across different industries (animal health, consumer, vaccines) or different drugs. A high dependence on one drug tends to weaken a company's moat; competitive threats, an emergence of an unknown side effect, or a patent loss can impair the cash flows from the drug, hurting the firm's ability to reinvest in developing the next generation of drugs.

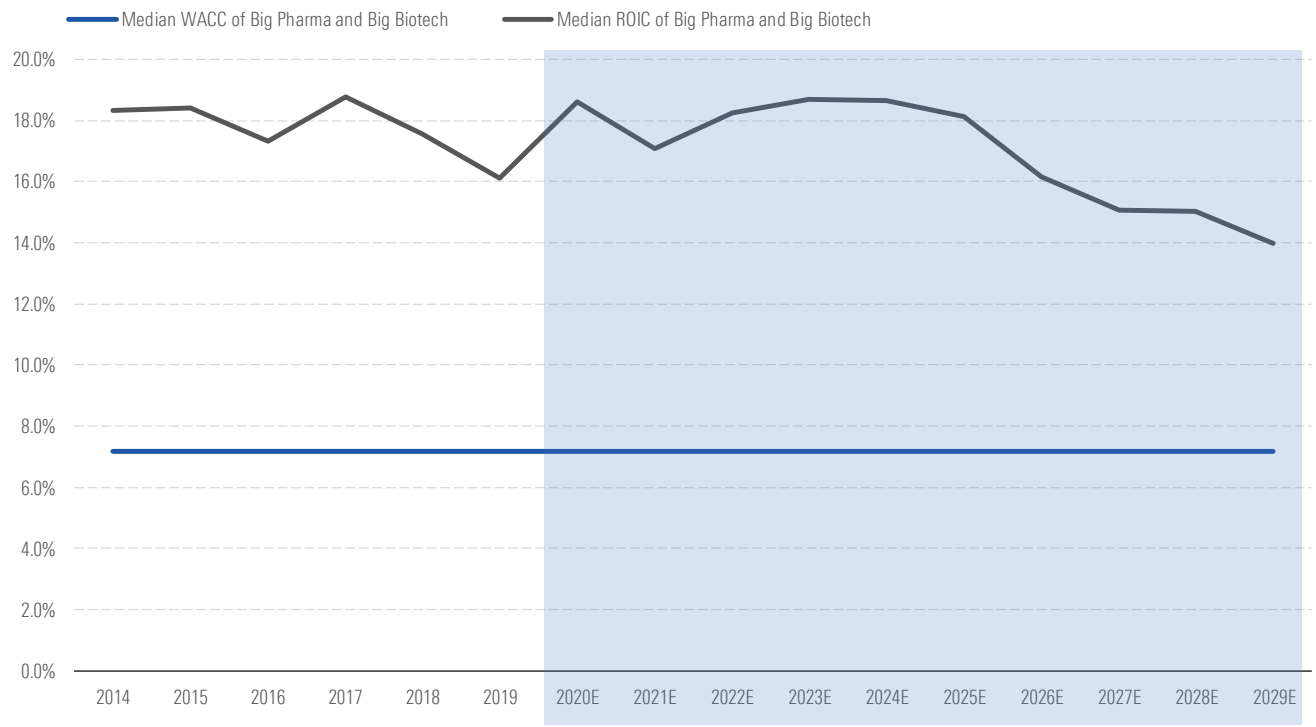
Most wide-moat firms do not depend on a single drug for a significant share of revenue; large drug firms that rely on a single drug--AbbVie (Humira) and Regeneron (Eylea)--hold narrow-moat ratings despite excess economic returns. For firms that are diversified across divisions, moats can be supported in several ways, including brand power (consumer, animal health), cost advantages (vaccines, animal health), and switching costs (animal health).

R&D Productivity Looks Largely Stable, Offsetting Patent Losses

The strong moats in the large drug and biotech firms look secure, with pipelines strong enough to offset patent losses. The industry will continue to face major patent losses; while the current landscape seems increasingly favorable for patent extensions--as shown by lengthening patent strategies used for immunology drug Humira, cancer drug Revlimid, and many other drugs--the eventuality of generic or biosimilar competition is certain. However, pipeline drug development is less certain with failures happening constantly. Nevertheless, the portfolio strategy of developing several new drugs supports the strong likelihood that next-generation drugs will successfully reach the market. Further, the shift toward developing drugs in areas of unmet medical need (rather than slight advancements in well-treated areas) suggests stronger pricing power for new drugs, a trend seen over the recent years, especially in cancer and rare-disease areas.

Based on our aggregate outlook for the large drug and biotech firms, we expect returns on invested capital to exceed weighted average cost of capital over the long term. In Exhibit 4, we show the historical ROICs of the group going back to 2014 along with our projections over the next decade. While the ROICs over the past five years haven't matched the very high ROICs of the early 2000s, the massive damage of the industry patent cliff in 2012-14 appears to have subsided, and the outlook for returns looks largely stable. Further, while we don't view another major patent cliff emerging because of more dispersed patent losses for the group, several very important patent losses will occur over the next five years, including Humira and Revlimid (agreements with generic/biosimilar competitors should spread out the damage for these drugs over several years based on royalty agreements and different competitive timing by geographic regions). Nevertheless, we see a mild decline in ROICs in the later years of our projections. Some of this decline is due to the lost visibility of new pipeline drugs that should emerge in five to seven years but are current in early-stage development with very little published clinical data (very little data to justify inclusion in our models). Overall, the spread of over 700 basis points between projected ROICs and WACC looks secure to support our moat ratings.

Exhibit 4 ROIC Versus WACC at Large Drug and Biotech Firms: Support for Strong Moat Ratings



Source: Morningstar, company reports.
Note: Firms included: AbbVie, Amgen, AstraZeneca, Bayer, Biogen, Bristol, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche, and Sanofi.

COVID-19 Impact on Underlying Pharma/Biotech Growth Looks Minimal

As we detailed in our report, "Coronavirus Causes Limited Impact to Big Pharma and Big Biotech," we lowered our fair value estimates by almost 2% in aggregate for Big Pharma and Big Biotech firms in early April, after factoring in the economic slowdown and disruption in use of drugs, vaccines, and consumer healthcare products due to the COVID-19 pandemic. We model near-term disruptions in drug utilization (particularly for drugs administered in hospitals) as well as delays in clinical trials and delayed or less effective new drug launches, but highly inelastic demand for most drugs should offset most recessionary impacts and prevent any moat erosion or long-term impact on pipeline potential from the pandemic.

Exhibit 5 Pandemic Impact to Long-Term Profitability at Large-Cap Branded Drug Firms

	Fair Value Estimate		5-year EPS CAGR			
Company (Ticker)	Pre-Pandemic	April 6	Pre-Pandemic	April 6	Portfolio Analysis	Sources of Payer Mix Risk (Medicaid)
AbbVie (ABBV)	$101	$97	0%	0%	Botox and new drugs Rinvoq and Skyrizi face headwinds	Humira
Amgen (AMGN)	$221	$219	4%	4%	Cardiology, osteoporosis ramps could slow, but late-stage pipeline not delayed	Enbrel
AstraZeneca (AZN)	$46	$44	16%	15%	Slower growth for cardiometabolic drugs and recently launched cancer drugs	
Bayer (BAYRY)	$29	$27	7%	6%	New indications for Xarelto track slower without sales support	
Biogen (BIIB)	$421	$413	2%	1%	MS base and aducanumab filing look safe, but Spinraza treatment and trial delays	Avonex
BioMarin (BMRN)	$119	$119	84%	67%	Palynziq could see slower growth, but val-rox, vosoritide see strong 2021 launch potential	
Bristol-Myers (BMY)	$64	$64	10%	9%	More limited impact to the cancer focused company	
GlaxoSmithKline (GSK)	$48	$42	1%	1%	Exchange rates caused the majority of the fair value change	Respiratory
Gilead (GILD)	$84	$82	5%	4%	Despite remdesivir potential, Descovy PrEP switch and filgotinib launch are likely delayed	
Johnson & Johnson (JNJ)	$137	$133	5%	5%	Elective procedures in orthopedics weigh on overall growth	
Eli Lilly (LLY)	$135	$130	14%	13%	New patient starts on Trulicity and Taltz creates mild challenges	Insulin
Merck (MRK)	$103	$103	9%	9%	Critically needed drugs like Keytruda and Gardasil shouldn't face long-term impacts	Januvia
Novartis (NVS)	$94	$91	5%	5%	New patient starts on Cosentyx and Entresto set up manageable pressures	
Novo Nordisk (NVO)	$54	$54	7%	7%	Rybelsus launch slowed, but overall diabetes business looks well protected	Insulin
Pfizer (PFE)	$46	$44	6%	5%	Prevnar utilization likely slows by adult patient population	
Regeneron (REGN)	$389	$421	7%	8%	Eylea, Dupixent headwinds are outweighed by coronavirus drugs Kevzara, novel antibodies	
Roche (RHHBY)	$49	$48	5%	5%	Hospital-administered drugs and diagnostics hit, but coronavirus tailwind (Actemra, diagnostics)	
Sanofi (SNY)	$57	$55	5%	4%	Dupixent growth likely slows as new patients delay treatment	Insulin

Source: Morningstar, company reports.

While access to drugs should normalize slowly throughout the year, and certainly in 2021 if a vaccine becomes widely available, changing payer mix could create more headwinds for drug firms next year. However, we don't include a hit from a shift to Medicaid in our valuation models, as we see a combination of types of job losses, transitional insurance options, improving economic conditions, and drug firm portfolio and geographic diversification preventing significant impacts.

Job Losses Include Many Who Already Lacked Strong Health Insurance Options

First, we assume that many of the jobs lost initially during the pandemic, such as jobs in the service industry (retail and restaurants), were unlikely to offer strong (or any) health coverage to begin with. Many of these Americans were likely already on more affordable exchange plans, something Eli Lilly discussed in its first-quarter earnings call. The shift of these Americans from no coverage or exchange coverage to Medicaid would have less of an impact on drug sales than the loss of patients from employer-sponsored health plans.

Employment in the U.S. is down by nearly 20 million jobs since February, as of the end of May. Kaiser recently estimated that of the nearly 78 million people who lived in a family with someone who lost a job in March or April, 61% (48 million) were covered by employer-sponsored insurance before the pandemic led to job loss. Of these Americans, 27 million lost healthcare coverage as a result (unable to switch to a spouse's insurance plan or to Medicare, for example), and 13 million are eligible for Medicaid, growing to 17 million eligible by January 2021 as unemployment insurance benefits end for most.[1]

Transitional Coverage Delays the Move to Medicaid

Newly unemployed who had previously been covered by employer-sponsored plans could begin with transitional coverage (COBRA), which can last up to 18 months, or unemployment insurance (most of unemployment insurance benefits will be exhausted in 2020). Therefore, we expect minimal impact from Medicaid switching in 2020. We expect these Americans to eventually switch to exchange plans or, if they qualify, to Medicaid, which reimburses drugs at lower prices than private plans and could pressure drug firm sales. Kaiser's data (as of 2018) estimates that 49% of Americans were on employer-sponsored insurance,[2] meaning, if all 17 million newly eligible switched to Medicaid in 2021, this percentage could fall by 5 percentage points, to 44%. This would be significantly above the shift that drug firms witnessed during the Great Recession; overall, AbbVie saw a 2-percentage-point increase in exposure to Medicaid between 2007 and 2009.

Economic Improvements Could Lower Exposure in 2021 and Beyond

Moody's projects annual job losses around 8 million by the end of 2020,[3] which would be a significant improvement from end-of-May numbers and allow many to avoid the transition to Medicaid. We expect further improvement in 2021 and beyond to reduce Medicaid enrollment and the related headwind on drug sales.

1 https://www.kff.org/coronavirus-covid-19/issue-brief/eligibility-for-aca-health-coverage-following-job-loss/

2 https://www.kff.org/other/state-indicator/total-population

3 https://www.wsj.com/articles/may-jobs-report-coronavirus-2020-11591310177

Drug Firm Portfolio and Geographic Diversification Can Shield From Payer Mix Risk

Assuming that the economy does not improve and we do see significant numbers of Americans enroll in Medicaid in 2021, exposure at drug firms is likely to vary significantly. The most exposed firms would be those with previously high levels of patients on employer-sponsored insurance (this is the category with the most pricing power to lose), and those that have a history of taking significant annual price increases (because of Medicaid's inflation rebate rules that limit price increases). Some older branded drugs have Medicaid rebates approaching 100%, making certain Medicaid sales minimally profitable. Insulin (Eli Lilly, Novo Nordisk, Sanofi), immunology drugs (AbbVie's Humira, Amgen's Enbrel), and respiratory drugs (Glaxo) could be among the most exposed to such a shift.

We modeled Novo Nordisk as an example of a firm with what we see as relatively high exposure to payer mix shift. Novo Nordisk currently sees 11% of total sales from U.S. insulin, 28% of total sales from U.S. GLP-1. If we assume that Novo Nordisk essentially loses all insulin sales (assume 100% Medicaid rebate) and half of GLP-1 sales (assume 50% additional rebates beyond private insurance levels) from the privately insured U.S. patients who could switch to Medicaid (assuming 17 million eligible, or 5% of Americans), this amounts to a total 1.5% impact on sales. We see this as an upper limit on potential sales impact for our firms, given Novo Nordisk's high exposure and the likelihood for improving unemployment levels in 2021 and beyond.

Beyond Novo Nordisk, Glaxo and Sanofi have relatively low exposure to U.S. sales (less than a third of total sales), which should protect from payer mix risk, while Amgen and AbbVie have relatively high U.S. exposure (more than two thirds of total sales), making the impact of Medicaid coverage changes slightly higher. For the full spectrum of exposure to U.S. branded drugs sales by firm, please see our report, "How ESG Risk Affects Moats and Valuation in Pharma and Biotech: Morningstar and Sustainalytics Offer Complementary Methodologies."

International Pricing to Fall Post-COVID-19, but Decline Limited by Already Low Overall Pricing

We expect to see a pricing impact on drugs outside the U.S. due to the pandemic, perhaps as early as 2021, as budgets are broadly squeezed. Even though we already assume low-single-digit pricing pressure annually in Europe (built into contracts with pharma and biotech firms), we expect countries to increasingly work together to negotiate prices. Budgets will no doubt be tighter following COVID-19 stimulus programs, and unlike the U.S., drug prices have a hard ceiling due to balanced budget requirements. That said, pricing is already quite low relative to the U.S.; even including an average 43% U.S. price discount from list prices (see our April 2019 piece, "No Drug Industry Moat Impact From Rebate Overhaul"), Morningstar's own analysis of rebates and individual analysis of net pricing of top revenue-generating drugs gets us to prices in the other developed markets that are roughly half that of U.S. net prices.

Significant U.S. Drug Pricing Policy Change Unlikely in 2020; Biden's Reforms Likely to Be Moderate

Although a big-picture healthcare issue still remains uncertain--the ACA is being debated at the level of the U.S. Supreme Court, with a decision whether the rule should be overturned expected by next spring --we think Joe Biden's moderate position and status as the presumptive Democratic nominee for president reduces the likelihood of significant drug pricing policy changes, despite more-aggressive reform recommendations from the Biden-Sanders unity task force. This also reduces the likelihood of a major policy-related impact on drug innovation. We see a less-than 10% probability of a "Medicare for All" system within the next decade, and this is not included in our analysis. Such a system would reduce U.S. drug prices with the negotiating power of a one-payer system, but odds are likely even slimmer following Biden's nomination over Bernie Sanders. The most likely-to-pass changes that could realistically influence drug pricing are still those encompassed in the Senate Prescription Drug Pricing Reduction Act bill, as described in Exhibit 6, but we still believe this holds a less-than 50% chance of passing, based on mixed support by both parties, and we haven't included the bill in our models. If passed, we estimate a 5% aggregate hit to U.S. branded drug sales from Medicare inflation price caps and Part D redesign.

We could still see some significant changes passed in 2020, but we think the likelihood is fading. The International Price Index, or IPI, and importation are two proposed rules that have yet to be finalized by the White House, but they are both likely experiencing delays due to the pandemic, and due to President Trump's uncertainty over the alternative of potential progress in the House and Senate with legislative reform. In terms of congressional action, funding was poised to expire in late May 2020 for various government healthcare programs, and this could have been a logical time to include drug pricing policy changes. However, this funding was extended through the end of November 2020 as part of the economic stimulus in the CARES Act, passed in March 2020, without addressing drug pricing.[4] Senate Finance Committee Chairman Chuck Grassley had recently been hopeful about a vote this year on drug price legislation, with the view that the pandemic is the perfect time to have a conversation about drug prices, as COVID-19 vaccine and treatment prices will be under intense scrutiny.[5] However, Grassley claimed in June 2020 that Democrats were unwilling to negotiate. According to Bloomberg and Politico, Grassley has the backing of Trump and at least a dozen GOP senators, and House Speaker Nancy Pelosi is willing to talk; however, Senate Majority Leader Mitch McConnell still has some issues with the

4 https://www.statnews.com/2020/04/14/states-drug-pricing-policies/

5 https://www.bloomberg.com/news/articles/2020-06-01/long-delayed-drug-price-legislation-not-dead-yet-grassley-says

PDPRA, and Senate Majority Whip John Thune sees potential for a scaled-back version of the bill, focused on limiting part D costs.

Turning to potential policy changes beyond 2020, presumptive Democratic presidential nominee Biden could provide an environment for incrementally more pricing pressure on drug firms, if elected, but we don't expect any major changes. The recommendations released from the Biden-Sanders unity task force in early July[6] look more aggressive than Biden's published stance on drug pricing reform, roughly encompassing most of the proposals in the House-passed HR3 bill. More disruptive pricing reform, such as broad international price benchmarking included in the HR3 bill and the task force recommendations, is extremely unlikely to be brought to vote in the Senate unless Democrats regain control in 2021. Even then, barriers to such reform include difficulty with bipartisan support, concerns about impact on innovation and access, and implementation.

Biden has historically supported innovation in the drug industry and has published views on pricing reform that are more moderate than those in the task force recommendation, leading us to doubt whether the task force's most aggressive and controversial recommendations would be prioritized. Other health care reforms--like expanding coverage with a public option--seem more critical, particularly during and following the pandemic. Biden and the unity platform both support importation (which we see as unlikely to impact pricing significantly, see Exhibit 6), and tax penalties on drugmakers for price increases north of inflation in Medicare and in Biden's public option plan (which is also part of the Senate PDPRA bill, and could have a 3% impact to sales, by our estimates). However, while Biden had historically supported giving Medicare the ability to negotiate drug prices, his position hasn't had the necessary teeth of former candidate Sanders' plan to establish a Medicare formulary that would allow pricing comparable to a basket of other countries.[7] Similarly, Biden has supported international price indexing, but to a more limited extent than the task force recommendations, in our view. Biden proposed that an independent review board established by the Department of Health and Human Services assess the value of newly launched specialty drugs that don't face competition, using prices in other countries as reference; this price would apply to Medicare, Biden's public option plan, and private plans that participate in the individual marketplace. In contrast, the task force recommends that these negotiated and benchmarked prices be applied to all purchasers, like the Sanders plan, making it more similar to HR3 (which extends prices from Medicare and Medicare Advantage to private plans, unless they opt out).

Exhibit 6 highlights some of the key areas of U.S. policy reform, current bills or proposed rules that could eventually be passed into law. We also include our estimates of impact to industry sales, and some of the most exposed and least exposed firms to various potential reforms. For details, please see our report, "How ESG Risk Affects Moats and Valuation in Pharma and Biotech: Morningstar and Sustainalytics Offer Complementary Methodologies."

6 https://joebiden.com/wp-content/uploads/2020/07/UNITY-TASK-FORCE-RECOMMENDATIONS.pdf
7 https://www.politico.com/newsletters/prescription-pulse/2020/03/10/biden-and-sanders-far-apart-on-drug-pricing-488528

Exhibit 6 Key Focus Areas for Drug Policy Reform, and Morningstar's Expectations for Impact to Drug Industry Sales

	International Reference Pricing	Medicare Inflation Caps	Medicare Part D Redesign/ Catastrophic Discounts	Importation	Medicare Part D Negotiation
Description	Lowering drug prices based on a basket of prices for the drug in markets outside the U.S.	Preventing drug firms from increasing prices at a rate higher than inflation.	Eliminating out-of-pocket costs during the high-cost catastrophic phase, and increasing drug firm responsibility for costs during this phase.	Allowing small molecule prescription drugs to be imported from Canada.	Repealing the law barring direct Medicare negotiation with drug firms on prices.
Vehicles to Policy Change	Executive branch (CMS/HHS): Medicare Part B international price index House: Elijah Cummings Lower Drug Costs Now Act (HR 3)	Senate: Prescription Drug Pricing Reduction Act (PDPRA, S. 2543) House: Elijah Cummings Lower Drug Costs Now Act (HR 3)	Senate: Prescription Drug Pricing Reduction Act (PDPRA, S. 2543) House: Elijah Cummings Lower Drug Costs Now Act (HR 3) House: Lower Costs, More Cures Act (HR 19)	Executive branch (HHS/FDA): Safe Importation Action Plan	TBD
Estimated Impact to Industry Sales	24%*	3%	2%	Not meaningful as proposed	Not meaningful as proposed
Least Exposed	Low U.S. Exposure Small Global Price Discrepancies GILD, BMRN, AZN	Low U.S. Exposure Low Medicare Exposure Small Annual Price Increases BMRN, GILD, GSK	Low U.S. Exposure Low Medicare Part D Exposure Low-Priced (<$10,000) Medicines NVO, SNY, LLY	Insulin, biologic, and IV drug-focused firms: RHHBY, NVO, AMGN, REGN	Low Part D Exposure: BMRN, REGN, NVS, RHHBY
Most Exposed	High U.S. Exposure Large Global Price Discrepancies ABBV, AMGN, BIIB	High U.S. Exposure High Medicare Exposure Large Annual Price Increases PFE, AMGN, ABBV	High U.S. Exposure High Medicare Part D Exposure High-Priced (>$10,000) Medicines PFE, BMY, ABBV	Small molecule drug focused firms: GILD, BMY, AZN, GSK	High Part D Exposure: BMY, GILD, NVO, ABBV
Analysis	White House could finalize rule at any time, but we view this as unlikely during the pandemic, and extent of impact is limited by Part B (hospital-based) focus. HR3 passed the House in December 2019 but is unlikely to gain Senate support.	PDPRA co-sponsors Grassley (Republican) and Wyden (Democrat) are having trouble getting support of Republican majority leader McConnell. HR3 passed the House in December 2019 but is unlikely to gain Senate support.	PDPRA co-sponsors Grassley (Republican) and Wyden (Democrat) are having trouble getting support of Republican majority leader McConnell. HR3 passed the House in December 2019 but is unlikely to gain Senate support. Bipartisan support for Part D redesign could allow HR 19 to pass Congress, but lacks wide Democrat support.	While the White House could finalize the rule at anytime, we think importation is difficult to effectively put into practice, as it's hard to reconcile with safety provisions preventing counterfeit drugs, and ensuring supply from Canada could be challenging.	Repeal of this law is unlikely to have a significant effect on pricing, due to the already high negotiating power of PBMs, unless paired with tougher pricing regulations.

Source: Morningstar, CBO (https://www.cbo.gov/system/files/2019-07/PDPRA_preliminary_estimate.pdf), CMS (https://www.cms.gov/Research-Statistics-Data-and Systems/Research/ActuarialStudies/Downloads/HR3-Titles-I-II.pdf).

*Assumed headwind for Medicare and private plan benchmarking. We assume a 25% probability that such a plan passes in our bear-case scenario. Overall, this leads to an 11% headwind in our bear case, when a 6% impact (25% probability of a 24% headwind) is combined with other potential policy changes (3% impact from Medicare inflation caps and 2% impact from Part D redesign).

The COVID-19 Treatment and Vaccine Pipeline: Accelerated Timeline, but Few Profit Opportunities

We expect the COVID-19 treatment landscape to evolve rapidly in 2020, with solid innovation supporting drug firm pipelines and moats. This support is less through direct sales of COVID-19 vaccines and treatments, and more through expected reduced efforts to lower drug prices at the potential expense of innovation. The dominance of Gilead's antiviral remdesivir in mid-2020 should shift to potential wide combination use with repurposed immunology drugs (including steroid dexamethasone, which recently showed a marked survival benefit in critically ill patients) in the third quarter, emergency use of some vaccines and targeted antibodies in the fourth quarter, and approval of several antibodies and vaccines by the end of 2020. We expect data by the end of the year showing whether oral antivirals combinations with Pfizer's protease inhibitor or Merck's EIDD-2801 improve on remdesivir alone. Exhibit 7 maps the potential progress for key vaccine, antiviral, repurposed immunology, and antibody programs.

Overall, we expect multiple approved vaccines by early 2021, with wide vaccination in developed markets by mid-2021. Vaccines are moving into trials and progressing into phase 3 more quickly than we anticipated (see our May 11 report), and three National Institutes of Health-sponsored phase 3 trials (likely around 30,000 patients each) are poised to start in July (Moderna), August (Astra), and September (Johnson & Johnson), according to a *Wall Street Journal* report based on conversations with NIH officials.[8] Pfizer and BioNTech's RNA-based program could move forward on a similar schedule once the firms determine which of four potential vaccines to pursue and at what dose; initial data in July was promising, and more data is expected throughout July that could lead to a phase 3 start by the end of the month. Novavax, which entered trials in May, brings another technology (antigen-based vaccine) to further diversify potential vaccine mechanisms, and CureVac's mRNA vaccine entered trials in June. Together with Merck (to enter phase 1 this year), these programs are all likely finalists in Operation Warp Speed, a partnership between the U.S. HHS and the Department of Defense that seeks to deliver 300 million doses of a vaccine to Americans by January 2021.

The length of time between phase 3 starts (where we have improving visibility) and widespread availability of a vaccine on the market is uncertain, but three vaccines look poised for potential emergency use authorizations this fall in the U.S., led by Astra/Oxford (September), Pfizer/BioNTech (October), and Moderna (November). Oxford has noted that if transmission is high, phase 3 results are

8 https://www.wsj.com/articles/coronavirus-vaccine-candidates-pivotal-u-s-testing-to-start-this-summer-11591781405

possible in a couple of months, but if transmission drops, it could take six months.[9] Therefore, these estimates seem reasonable assuming the firms are able to find regions of the U.S. and other countries with significant ongoing outbreaks, enroll trials rapidly, meet the FDA threshold of 50% efficacy, and avoid unexpected safety issues or findings of enhanced disease for vaccine recipients. We assume that emergency use authorization could be granted following phase 3 efficacy and safety data, but before the firm can file for and receive full FDA approval, in line with June 2020 FDA guidance.[10]

While profit from vaccines should be relatively minimal (we do not include them in our valuation models), we do include remdesivir (commercial supply expected in the second half of 2020) and select targeted antibodies (like Regeneron's REGN-COV2). We model sales of remdesivir peaking at $3 billion in 2021 and REGN-COV2 around $2 billion in 2021 and 2022 (see pages 80 and 142 for more details on our remdesivir and REGN-COV2 assumptions).

Exhibit 7 The COVID-19 Pipeline: Vaccines Could Begin to Receive Emergency Use Authorization Based on Phase 3 Data as Early as September 2020

	Timeline						
Firm/Treatment	**Enter Clinic (data)**	**Start Phase 3**	**Approval**	**Outside Funding**	**Expected dosage**	**2021 Capacity (Doses)**	**Expected Price**
Vaccines							
Moderna's mRNA-1273 (mRNA code for spike protein)	**March (Phase 1 top line data)**	**July**	**December (EUA)**	OWS: $483 million	Two doses, 100 ug each	500 million-1 billion (Lonza CMO, Catalent and Rovi fill/finish)	Less than pneumonia vaccine ($800)
Oxford/AstraZeneca's ChAdOx1 nCoV-19 (AZD1222) (viral vector w/ spike protein code)	**April (no clinical data)**	**August (UK Ph 2/3: May)**	**September (EUA)**	OWS ($1.2 billion), CEPI ($750 million), IVA (EUR 750 million), UK and US contracts	1 dose or 2 doses (5x10^10vp), four weeks apart	2 billion (OxfordBIoMedica in UK, Emergent CMO, Catalent CMO, Cobra, Symbiosis, Serum Institute: 1 billion in developing markets)	Not for profit
Pfizer/BioNTech's BNT162 b1, b2: modified mRNA (RBD, full spike protein) a1: uRNA for RBD c2: self amplifying RNA for full spike protein	**April (Phase 1/2 preprint, more data July 2020E)**	**July**	**October (EUA)**	none (focused on internal funding for speed)	1 dose at ~1 ug (self-amplifying), or 2 doses (21 days apart), 10ug-30ug (mRNA vaccine BNT162b1)	More than 1.2 billion, at multiple PFE facilities in the US (assuming 10-30 ug dose)	Similar to Moderna (in-line with other commercial vaccines)
J&J's Ad26.COV2-S (intranasal, viral vector w/ spike protein code)	**July**	**September**	**Q1 2021**	OWS: $456 million	TBD (booster 2-3 yrs later)	More than 1 billion (Emergent, Catalent CMOs)	Not for profit (around $10)
Novavax's NVX-CoV2373 (nanoparticle-bound spike protein antigen)	**May (July 2020E)**	**September**	**Q1 2021**	CEPI ($384 million), OWS ($1.6 billion)	1 dose or 2 doses, 5-25 ug	More than 1 billion (Praha vaccines acquisition)	
CureVac's CVnCoV (self-amplifying mRNA based on spike protein)	**June**	**October**	**Q1 2021**	CEPI, European Commission, Kreditanstalt fur Wiederaufbau (German state bank)	2-8 ug	Several hundred million, Germany facility	
Sanofi/Glaxo (Spike protein antigen)	**September**	**Early 2021**	**Mid-2021**	BARDA, pending UK contract	TBD	1 billion (with Glaxo's adjuvant)	

Source: Morningstar, company reports. OWS: Operation Warp Speed, EUA: Emergency Use Authorization, RBD: receptor binding domain
*other clinical-stage vaccine programs (with smaller manufacturing capabilities) include: Imperial/Morningside's self-amplifying mRNA (entered trials in June, tens of millions of doses in 2021), Inovio's DNA plasmid INO-4800 (to enter phase 2/3 summer 2020, 1 million doses by end of 2020), CanSino's adenovirus vector (entering phase 3, 70-80 million doses a year), Sinovac's inactivated virus CoronaVac (entered phase 3 in July in Brazil, 100 million a year), Sinopharm's inactivated virus BBIBP-CorV (phase 1/2, 200 million a year), China's Institute of Medical Biology inactivated virus (phase 2), Clover's SCB-2019 with Glaxo or Dynavax adjuvant (entered phase 1 in June, data expected August and Phase 2/3 start by year end), Medicago/Glaxo's CoVLP (entering phase 1 in mid-July 2020, 100 million doses in 2021).

9 https://www.ox.ac.uk/news/2020-05-22-oxford-covid-19-vaccine-begin-phase-iiiii-human-trials

10 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

Exhibit 7 (continued) The COVID-19 Pipeline: Antivirals, Repurposed Immunology, and Targeted Antibodies Support Diverse Fight Against COVID-19

	Timeline			
	Enter Clinic	Start Phase 3	Approval	Morningstar Analysis
Antivirals				
Gilead's remdesivir	March	March	May EUA Mid-2020E Approval	We expect commercial supply leading to sales in the second half of 2020. Inhaled remdesivir could have data (non-hospitalized patients) in August, and combination with Olumiant in ACTT-II could have data this summer.
Merck/Ridgeback's EIDD-2801	April	August	Q4 2020	Oral dosing could give this broader applicability than remdesivir, but it could also be used in combination (both block RNA polymerase in different ways). Ridgeback could have a million courses by fall.
Pfizer's protease inhibitor	August	October	Early 2021	Pfizers SARS-CoV-2 3C-like (3CL) protease inhibitor is poised to start trials in the third quarter and could also be effective in combination with remdesivir or EIDD-2801.
Repurposed Immunology				
Roche/Actemra	March	March	August	Roche expects data in July, and is starting official combination phase 3 studies in June with remdesivir, although the failure of Sanofi/Regeneron's similar drug Kevzara doesn't bode well.
Incyte/Novartis (Jakafi)	April	April	August	Jakafi data in July could indicate whether the drug could reduce severity of patient immune reactions.
Incyte/Lilly (Olumiant)	April	April	August	NIH study ACTT-2 (likely data in July) tests a combination with remdesivir. A new phase 3 study of Olumiant alone (in hospitalized patients not on ventilation) started in mid-June.
	Timeline			
	Enter Clinic	Start Phase 3	Approval	Morningstar Analysis
Targeted Antibodies				
Convalescent plasma/ Hyperimmune globulins (Grifols, Plasma alliance**)	March/July	July/September	September/ November	Convalescent plasma (donated by recovered patients) is being directly given to severely ill patients, and several large studies (Mayo Clinic) are in progress. This plasma is also being used to make concentrated antibodies, with Grifols entering trials in July and the Plasma Alliance this summer. Supply is limited; 1-2 units of convalescent plasma are required for each patient, and 2-3 units per donation--hyperimmunes require even more donations.
Regeneron's REGN-COV2 (REGN10933+REGN10987 cocktail)	June	July	October	Regeneron started an adaptive phase 1/2/3 trial in June in hospitalized and non-hospitalized COVID-19 patients, and a NIAID-partnered prevention study (in high-risk individuals with close exposure to infected patients) began in July. We expect initial safety and efficacy data by the end of summer, and a $450 million OWS contract secures hundreds of thousands of doses for the U.S. this fall.
Lilly/Abcellera's LY-CoV555	June	October	December	LY-CoV555 entered its first study in June in hospitalized patients, with data expected in July 2020, and phase 2 expected to focus on non-hospitalized patients and prevention.
Lilly/Junshi's JS016	June	October	December	Lilly's other antibody program entered phase 1 in China in June and is poised to enter phase 1 in the US in healthy volunteers in June as well.
Vir/Glaxo	July	October	December	Vir expects to start trials this summer, working with Glaxo on VIR-7831 and VIR-7832.
AstraZeneca	August	December	Early 2021	Astra expects to be in testing this summer, with two candidates from its Vanderbilt agreement.
Amgen/Adaptive	September	Early 2021	Mid-2021	April partnership poised to send candidates to Amgen for development within six months, could make tens of millions of doses starting in 2021.

Source: Morningstar, company reports. OWS: Operation Warp Speed, EUA: Emergency Use Authorization

**Plasma alliance includes CSL, Biotest, BPL, LFB, Octapharma, Takeda, ADMA Biologics, BioPharma Plasma, GC Pharma, and Sanquin.

M&A Through 2024: Most Likely to Continue to Focus on Midsize Deals

Among the major acquisitions of the past 20 years, the key motivations for acquiring companies have been cutting costs (Pfizer's acquisition of Wyeth and Merck's acquisition of Schering-Plough), adding growth (Pfizer's acquisitions of Warner Lambert and Pharmacia), and replenishing pipelines (Bristol's acquisition of Celgene). Motives around diversification have sent mixed signals, with AbbVie looking for diversification in Allergan versus the many divestments from Big Pharma, including animal health, consumer health and noncore therapeutic areas. This gives us less clarity on how firms want to position themselves through corporate actions.

However, we think more-focused strategies are likely to dominate in M&A philosophy over the next few years over more diversified ones. Analyzing the large deals of the past decades, value creation was rarely achieved, and these acquisitions tended to capture most of management efforts, leaving less focus on innovation. As a result, we expect most deals to focus on smaller firms that can be tucked into operations more easily with a focus on innovative new drugs. However, the most important factor in all acquisitions is price, which tends to be higher for the smaller firms as acquisition premiums are placed on valuations. Therefore, we still expect firms to make larger acquisitions, like Bristol's acquisition of Celgene to gain innovative pipeline assets. Also, we see several firms that have had healthy share price performance, allowing them to issue shares to pay for larger deals if necessary. Amgen, Astra, and Regeneron are prime examples of firms that will potentially leverage stock price gains in a larger acquisition.

Among large-cap targets, we think Regeneron looks appealing, given its strong bispecific antibody pipeline in oncology and recently reduced investment from long-time partner Sanofi. Among smaller-cap targets, we think several oncology targets could be logical additions for their large-cap partners in combination therapy, like Seattle Genetics (Bristol's Opdivo with Adcetris in Hodgkin's lymphoma), Nektar, (Bristol's Opdivo with bempegaldesleukin in multiple cancers), and Exelixis (Roche's Tecentriq with cabozantinib in multiple cancers). We also see RNA-focused firms like Moderna (Merck collaboration) and BioNTech (Pfizer and Roche collaborations) being logical targets, as technology is currently being validated with SARS-CoV-2 vaccines in clinical testing at a much more rapid pace than expected. Alexion has been under pressure to pursue a sale from key investors, and Gilead and Roche (both focused on building immunology exposure) could be logical buyers, although we see this as less likely than some other potential deals. Intercept looks appealing for its ability to allow a firm to lay the groundwork in NASH commercialization with obeticholic acid up for approval this year (Gilead and Novo

Nordisk could be logical buyers). Momenta also looks particularly appealing as one of the leaders in the FcRn antibody market, which could serve multiple autoimmune markets; Amgen, Gilead, Regeneron, or Roche could all be interested in Momenta's pipeline.

Exhibit 8 Future Drug Industry M&A: Mapping the Likely Fits Between Acquirers and Targets

			Key Targets								
				Amgen (AMGN)	**AstraZeneca (AZN)**	**Biogen (BIIB)**	**Bristol (BMY)**	**Gilead (GILD)**	**Eli Lilly (LLY)**	**Regeneron (REGN)**	**Smid-cap targets** (focus, market cap)
		Motivation: Rationale		Sell at a Premium Multiple	Sell at a Premium Multiple	De-risk Alzheimer's Platform	De-risk Pipeline and Patent Losses	Sell at a Premium Multiple	Sell at a Premium Multiple	Sell at a Premium Multiple	
			Mkt Cap $B	151	138	44	136	96	160	64	
Key Acquirers	**Amgen (AMGN)**	**High:** Aging Products and Modest Pipeline	151		Immunology partners, oncology complementary	Builds neuro beyond Aimovig	Cardiology, oncology complementary (psoriasis anti-trust issues)	Immunology, oncology complementary	Diabetes a poor fit for Amgen	PCSK9 anti-trust issues, bispecifics duplication	**Incyte** (oncology, immunology, $23B) **Momenta** (immunology, $4B) **BioMarin** (rare disease, $23B) **Clovis** (oncology, $1B)
	AstraZeneca (AZN)	**Low:** Strong Portfolio and Limited Patent Losses	138	Cardiology, oncology look complementary		Historical interest in neurology	Heavy overlap in oncology and likely too large	Expands immunology footprint	Good fit, but likely too large	Fits with Astra's growth profile, but PD-1/PD-L1 anti-trust issues	**Seattle Genetics** (oncology, $30B)
	Bristol-Myers (BMY)	**Medium:** Strong Pipeline, but Major Patent Losses	136	Cardiology, oncology complementary (psoriasis anti-trust issues)	Heavy overlap in oncology and likely too large	Risky buy, but could help offset patent losses		Expands immunology, oncology pipeline, lessens patent losses	Good fit, but likely too large	Lessens patent pressures, but PD-1/PD-L1 anti-trust issues	**Bluebird** (oncology, rare disease, $4B) **Nektar** (oncology, $4B) **Seattle Genetics** (oncology, $30B) **Clovis** (oncology, $1B)
	Gilead (GILD)	**High:** Declining Hep. C drugs and Modest Pipeline	96	Too large (see Amgen-Gilead)	Too large (see Astra-Gilead)	Tuck-in neurology arm	Too large (see Bristol-Gilead)		Too large (see Lilly-Gilead)	Oncology fit (adds PD1, bispecifics)	**Momenta** (immunology, $4B) **Galapagos** (immunology, $13B) **Alexion** (rare disease, $25B)
	Johnson & Johnson (JNJ)	**Low:** Mild Patent Losses and Improving Internal Pipeline	377	Poor fit ex-immunology, TNF anti-trust issues	Oncology fit, but BTK anti-trust issues	Tuck-in neurology arm	Oncology/ immunology fit	HIV/ oncology/ immunology fit	Adds growth, but IL23 anti-trust issues	Oncology fit (adds PD1, bispecifics)	**Genmab** (oncology, immunology, $22B)
	Eli Lilly (LLY)	**Low:** Mild Patent Losses and Strong Growth Outlook	160	Good fit, but likely too large	Good fit, but likely too large	Strong interest in Alzheimer's	Good fit, but likely too large	Immunology (JAK) anti-trust issues, virology outside Lilly's focus		Oncology fit (adds PD1, bispecifics)	**Clovis** (oncology, $1B) **Incyte** (oncology, immunology $23B)
	Merck (MRK)	**Medium:** Strong Growth Potential, but Weak Pipeline	201	AMGN oncology pipeline adds to Keytruda	Poor fit, PD-1/L1 ant-trust issues	Tuck-in neurology arm	PD-1 product overlap	CAR-T interest, but HIV overlap	Oncology, diabetes fit	PD-1 anti-trust issues, but adds combo drugs	**Moderna** (infectious disease, oncology, $23B)
	Novartis (NVS)	**Medium:** Major Patent Losses, but Solid Pipeline	202	Neurology partners, boosts oncology pipeline	Oncology fit	Anti-trust issues in MS, SMA	CAR-T anti-trust issues	CAR-T anti-trust issues	Anti-trust issues in immunology (IL17, CGRP)	Anti-trust issues in ophthalmology	**Ionis** (multiple therapeutic areas, $8B) **Clovis** (oncology, $1B) **Incyte** (oncology, immunology $23B)
	Roche (RHHBY)	**Medium:** Strong Growth Potential, but Biosimilar Pressures	300	Duplicates bispecific efforts	PARP/blood cancer/asthma fit, but PD-L1 anti-trust issues	Neurology anti-trust issues	PD-1/L1 anti-trust issues	Pricey entry into CAR-T: virology outside Roche's focus	Oncology fit, but diabetes outside Roche focus	Anti-trust issues (ophthal, oncology, immunology)	**BioNTech** (oncology, $15B) **Exelixis** (oncology, $7B) **Momenta** (immunology, $4B)
	Sanofi (SNY)	**Medium:** Steady Growth, but Weak Pipeline	129	Likely too large, out of Sanofi's focus	Good fit, but likely too large	Tuck-in neurology arm	Good fit, but likely too large	Virology doesn't fit with Sanofi's focus	Potential anti-trust issues in diabetes	Divested a major stake	**Clovis** (oncology, $1B) **Alexion** (rare disease, $25B) **BioMarin** (rare disease, $23B) **UCB** (immunology, $20B)

Rational combination
Less likely combination
Very unlikely combination

Source: Morningstar, company reports. Market cap data as of July 6, 2020.
Note: We see debt-heavy firms (AbbVie, Bayer, GlaxoSmithKline, and Pfizer) as less likely to acquire or be targets.

Key Catalysts Through 2021: Several New Launches Possible at Amgen and Bristol

Big Pharma and Big Biotech firms tend to have significant stock price moves with clinical data and drug approvals. While Morningstar and market forecasts probability-weight future events, the actual outcome is often a catalyst for share movement as estimates change and uncertainty around those estimates declines. We see a healthy number of catalysts through the end of 2021 among big pharma and big biotech firms in a variety of indications, supporting pipeline productivity and economic moats.

While each event listed in Exhibit 9 (upcoming approvals) and Exhibit 10 (upcoming data) has a different level of magnitude of importance, we see several important events for Amgen and Bristol through 2021, in particular. Amgen could see key data in late 2020 and approvals in 2021 for three key therapies: sotorasib (lung cancer), omecamtiv mecarbil (heart failure), and tezepelumab (asthma). Bristol is in a position to see several approvals stemming from its 2019 acquisition of Celgene, following on the heels of the recent approval of Zeposia (ozanimod) in multiple sclerosis. Through 2021, we expect approval of three key blood cancer therapies, including CC-486 and CAR-T therapies liso-cel and bb2121. Bristol will see blood cancer competition from rivals including J&J's JNJ-4528 (2021E approval) and Glaxo's belantamab (2020E approval), and in MS from J&J's ponesimod (2020E approval) and Novartis's ofatumumab (2020E approval).

Biogen is also at a critical point for its aducanumab program, which was filed with the FDA in July 2020 and should receive an FDA decision in 2021; while we only model a 40% probability of approval, we do model a 20% probability of approval of Roche's similar drug gantenerumab (phase 3 data 2021E), and see efficacy of Novo Nordisk's GLP-1 therapies as a wild card (liraglutide data expected in 2020).

Novo Nordisk and Eli Lilly will continue to face off in the GLP-1 market, as Novo Nordisk hopes to produce high-dose Ozempic data to match recent strong data for high-dose Trulicity, and both firms look to improve on this with combination regimens (Eli Lilly's GIP/GLP tirzepatide should have data in 2020-21E).

BioMarin is also at a critical point for its rare disease pipeline, with hemophilia A gene therapy Roctavian and achondroplasia therapy vosoritide poised for launches over the next year.

Oncology and immunology remain two key areas for new data. In oncology, we will also see some of the first key data in adjuvant lung indications come through for PD-1/PD-L1 antibodies, including Astra's

Imfinzi (2021E), Merck's Keytruda (2021E), and Roche's Tecentriq (2021-22E). In immunology, AbbVie looks poised to expand its approval for JAK inhibitor Rinvoq as Gilead's filgotinib (arthritis), Pfizer's abrocitinib (atopic dermatitis), and Roche's etrolizumab (ulcerative colitis) could enter the market. There is also more head-to-head data coming in this space, with Rinvoq data versus Dupixent expected in early 2021 in atopic dermatitis, Stelara data versus Humira in Crohn's coming in 2020, and Bristol's BMS-986165 versus Otezla in psoriasis expected in late 2020.

Exhibit 9 Key Catalysts Through 2021: Potential Approvals ($ in Millions)

Firm	Drug	Indication	Timing	2024E Sales	2024E Consensus
AbbVie	Rinvoq	psoriatic arthritis, atopic dermatitis, ankylosing spondylitis	2021	3,000	3,000
Amgen	Sotorasib	lung cancer	2021	400	600
Amgen	omecamtiv mecarbil	heart failure	2021	400	500
Amgen/Astra	tezepelumab	asthma	2021	650	600
AstraZeneca	Tagrisso	adjuvant lung cancer	2020	7,700	7,100
AstraZeneca	anifrolumab	lupus	2021	300	200
AstraZeneca	roxadustat	anemia	2020	600	900
Biogen	aducanumab	Alzheimer's	2021	1,800	2,500
BioMarin	vosoritide	achondroplasia	2021	1,100	550
BIoMarin	Roctavian	hemophilia A	H2 2020	1,100	750
Bristol	Liso-cel	blood cancer	2020	1,200	800
Bristol	CC-486	blood cancer	2020	1,100	600
Bristol	bb2121	blood cancer	2021	700	900
Gilead	filgotinib	rheumatoid arthritis	H2 2020	1,600	1,000
Gilead	Veklury (remdesivir)	COVID-19	mid-2020	2,500 (2021)	1,400 (2022)
GlaxoSmithKline	Trelegy	asthma	2021	1,400	2,400
GlaxoSmithKline	fostemsavir	HIV	2020	200	300
GlaxoSmithKline	cabotegravir	HIV	2020	700	700
GlaxoSmithKline	belantamab	multiple myeloma	2020	400	800
Johnson & Johnson	Tremfya	psoriatic arthritis	2020	2,900	3,000
Johnson & Johnson	ponesimod	multiple sclerosis	2020	500	200
Johnson & Johnson	JNJ-4528	blood cancer	2021	1,100	NA
Eli Lilly/Pfizer	tanezumab	pain	2020	600	300
Eli Lilly	mirikizumab	psoriasis	2020	800	600
Merck	V114	pneumococcal vaccine	2021	400	600
Merck	gefapixant	cough	2020	200	300
Novartis	ofatumumab	multiple sclerosis	2020	1,300	1,700
Novartis	inclisiran	cholesterol lowering	2021	600	1,100
Novo Nordisk	Ozempic	obesity	2021	800 (obesity)	800 (obesity)
Pfizer	abrocitinib	atopic dermatitis	2021	700	400
Pfizer	Prevnar 20 (adult)	pneumococcal vaccine	2021	6,200	6,200
Regeneron	Libtayo	lung cancer (monotherapy)	2021	990	1,288
Regeneron	REGN-COV2	COVID-19	H2 2020	2,000 peak (2021-22)	NA
Roche	Lucentis: port delivery system	nAMD	2021	1,400 (total Lucentis)	1,200 (total Lucentis)
Roche	etrolizumab	ulcerative colitis	2021	700	650
Roche	ipatasertib	prostate cancer, breast cancer	2021	480	650
Roche	satralizumab	NMOSD	H2 2020	350	370
Roche	risdiplam	SMA	H2 2020	700	1,300

Source: Morningstar, company reports.

Exhibit 10 Key Catalysts Through 2021: Clinical Data ($ in Millions)

Firm	Drug	Indication	Timing	2024E Sales	2024E Consensus
AbbVie/Roche	Imbruvica/Venclexta	CLL	2021	7,100*	7,800
AbbVie/Roche	Venclexta	t(11;14) positive multiple myeloma	2021	2,900	2,800
AbbVie	Rinvoq	atopic dermatitis (head to head vs. Dupixent)	Early 2021	3000	3000
Amgen	AMG 701	multiple myeloma	H2 2020	500	100
Amgen	Sotorasib	lung cancer	H2 2020	400	600
Amgen	omecamtiv mecarbil	heart failure	H2 2020	400	500
Amgen/Astra	tezepelumab	asthma	H2 2020	650	600
AstraZeneca/Merck	Lynparza	all comers prostate cancer	2021	3,300	3,600
AstraZeneca	Calquence	CLL (head to head vs. Imbruvica)	2021	2,100	2,200
AstraZeneca	Imfinzi	first line lung	2021	5,500	4,100
AstraZeneca	Imfinzi	adjuvant lung	2021	5,500	4,100
Bayer	finerenone	Diabetic Kidney Disease	late 2020	400	300
Biogen	opinicumab	multiple sclerosis	mid-2020	350	100
Biogen	tofersen	ALS	2021	150	150
Biogen	Timrepigene emparvovec	choroideremia	late 2020	250	150
Bristol	BMS-986165 v Otezla	Moderate/Severe Psoriasis	H2 2020	BMS-986165: 500 Otezla: 3,000	BMS 986165: 100 Otezla: 3,200
GlaxoSmithKline	daprodustat	kidney disease	2020/2021	300	300
Johnson & Johnson	Stelara	Crohn's: Head to head versus Humira	2020	9,800	9,400
Eli Lilly	lebrikizumab	atopic dermatitis	2021	900	200
Eli Lilly	Jardiance	heart failure	2020	1,800	1,900
Eli Lilly	Mirikizumab	psoriasis	2021	800	600
Eli Lilly	tirzepatide	diabetes	2020/2021	500	1,100
Merck	V114	pneumococcal vaccine	late-2020	400	600
Merck	Keytruda	adjuvant lung	2021	24,400	21,500
Novartis	Ilaris	cancer	2021	2,000	900
Novo Nordisk	Ozempic-high dose	diabetes	Q4 2020	6,000	5,800
Novo/Lilly	Ozempic v tirzepatide	diabetes	2021	tirzepatide: 500	tirzepatide: 1,100
Novo Nordisk	liraglutide	Alzheimer's	2020	not modeled	NA
Novo/Gilead	semaglutide/ cilofexor/ firsocostat	NASH	Q3 2020	400 (in NASH)	NA
Pfizer	PF-06425090	RSV vaccine	Late-2020	750	NA
Regeneron/Sanofi	Libtayo	lung cancer--chemo combo	2021	990	1288
Regeneron	fasinumab	pain	H2 2020	290	NA
Regeneron	REGN5458/5459	multiple myeloma	ASH 2020	500	NA
Regeneron	REGN-COV2	COVID-19	summer 2020	2,000 (2021, 2022)	NA
Roche	Perjeta/Kadcyla	adjuvant HER2+ BC	H2 2020	6,600 combined	8,000 combined
Roche	Tecentriq	neoadj TNBC, ovarian cancer	H2 2020	11,300	6,400
Roche	Tecentriq	adjuvant/neoadjuvant NSCLC	2021	11,300	6,400
Roche	etrolizumab	ulcerative colitis	H2 2020	700	650
Roche	ipatasertib	prostate cancer, breast cancer	H2 2020	480	650
Roche	Polivy	1L DLBCL	late 2020/ early 2021	1100	1200
Roche/Sarepta	SRP-9001/RG6356	DMD	2021	100	300
Roche	gantenerumab	Alzheimer's	2021	350	150
Roche	faricimab	AMD, DME	2020-2021	225	300
Sanofi	fitusiran	hemophilia A/B	H2 2021	400	300
Sanofi	SERD-859	cancer	2021	300	NA

Source: Morningstar, company reports.

*Imbruvica sales to AbbVie.

Differentiated Forecasts: Immunology and Oncology Pipelines Look Underappreciated

When stacked against consensus, our forecasts tend to favor newer oncology and immunology programs over aging products facing potential branded or generic competition, which we think supports R&D productivity and economic moats for firms with healthy new product portfolios and/or solid pipelines. See Exhibit 11 for a list of some of the drugs we see as the most underappreciated, and Exhibit 12 for the drugs we see as the most overvalued.

Oncology is one of the key areas where our estimates differ from consensus, and we are generally more bullish than consensus in this market. In immuno-oncology, we think the potential for newer PD-1/PD-L1 therapies to grow new markets has been underappreciated, including Astra's Imfinzi (earlier-stage lung cancer) and Roche's Tecentriq (lung cancer, breast cancer, and liver cancer). Merck's leading drug Keytruda also looks undervalued, as the market is still undervaluing the overall opportunity for future growth, Keytruda should gain approvals in earlier-stage lung cancer and expand share, particularly internationally, over the next few years. In multiple myeloma specifically, we see more potential for bispecific antibodies targeting BCMA (such as Amgen's AMG 701, Regeneron and Sanofi's REGN5458/5459) than consensus, and less potential for Glaxo's antibody-drug conjugate belantamab (which should be earlier to market, but with weaker efficacy). Two established drugs in oncology look overvalued, as we expect faster generic erosion for Bristol's Revlimid and steeper competition for J&J/AbbVie's Imbruvica than consensus.

We see a similar theme in immunology, with several undervalued newer drugs and a handful of older therapies that should fade more rapidly than consensus predicts. For example, JAKs like AbbVie's Rinvoq and Pfizer's abrocitinib, as well as Eli Lilly's lebrikizumab, look strong in atopic dermatitis, and we expect them to take some share from Dupixent's dominant position. Gilead's filgotinib has significant potential in arthritis due to its strong safety profile, and Eli Lilly's Taltz also looks undervalued. However, we assume steeper declines for AbbVie's Humira, Amgen's Enbrel, and Bristol's Orencia as new competition and biosimilars hit the market over the next few years.

In cholesterol-lowering, we still see significant potential for Amgen to grow its Repatha franchise, which looks undervalued, and slower potential for inclisiran, which looks overvalued, to gain share, as we await long-term survival data.

Exhibit 11 Underappreciated Drugs: Morningstar 2024 Forecast Versus Consensus ($ in Millions)

Firm	Drug	Indication	2024E Sales	2024E Consensus
Amgen	Repatha	cholesterol-lowering	2,500	1,800
Amgen	AMG 701	multiple myeloma	500	100
AstraZeneca	Tagrisso	lung cancer	7,700	7,100
AstraZeneca	Imfinzi	cancer	5,500	4,100
AstraZeneca	Lokelma	hyperkalemia	1,000	500
BioMarin	vosoritide	achondroplasia	1,100	550
BloMarin	Roctavian	Hemophilia A	1,100	750
Bristol	CC-486	blood cancer	1,100	600
Gilead	Veklury (remdesivir)	COVID-19	2,500 (2021 peak)	1,400 (2022 peak)
Gilead	filgotinib	rheumatoid arthritis	1,600	1,000
Johnson & Johnson	Xarelto	cardiovascular	3,500	2,500
Johnson & Johnson	Erleada	cancer	2,700	1,800
Eli Lilly	Taltz	immunology	4,200	2,900
Eli Lilly	Verzenio	cancer	4,500	2,100
Eli Lilly	Lebrikizumab	immunology	900	300
Merck	Keytruda	cancer	24,400	21,500
Novartis	Ilaris	cancer	2,000	900
Pfizer/Lilly	Tanezumab	pain	700	200
Regeneron/Sanofi	REGN5458/5459	multiple myeloma	500	NA
Regeneron	REGN-COV2	COVID-19	2,000 peak (2021-22)	NA
Roche	Tecentriq	oncology	11,300	6,400

Source: Morningstar, company reports.

Exhibit 12 Overvalued Drugs: Morningstar 2024 Forecast versus Consensus ($ in Millions)

Firm	Drug	Indication	2024E Sales	2024E Consensus
AbbVie	Humira	immunology	6,200	9,800
AbbVie	Botox	cosmetic/therapeutic	4,200	4,800
Amgen	Enbrel	immunology	1,700	3,600
AstraZeneca	Pulmicort	COPD	1,100	1,600
Bayer	Eylea	ophthalmology	2,300	2,800
Biogen	aducanumab	Alzheimer's	1,800	2,500
Bristol	Orencia	immunology	2,000	2,700
Bristol	Revlimid	blood cancer	5,900	7,900
GlaxoSmithKline	Belantamab	multiple myeloma	400	900
Johnson & Johnson	Prezista	HIV	700	1,800
Johnson & Johnson	Invega line	Schizophrenia	3,100	4,700
Johnson & Johnson	Imbruvica	blood cancer	5,100	6,400
Johnson & Johnson	Spravato	depression	600	1,100
Eli Lilly	Tirzepatide	diabetes	500	1,100
Novartis	Inclisiran	cardiovascular	600	1,100
Pfizer	Vyndaqel	cardiovascular	2,200	2,800
Roche	risdiplam	SMA	700	1,300

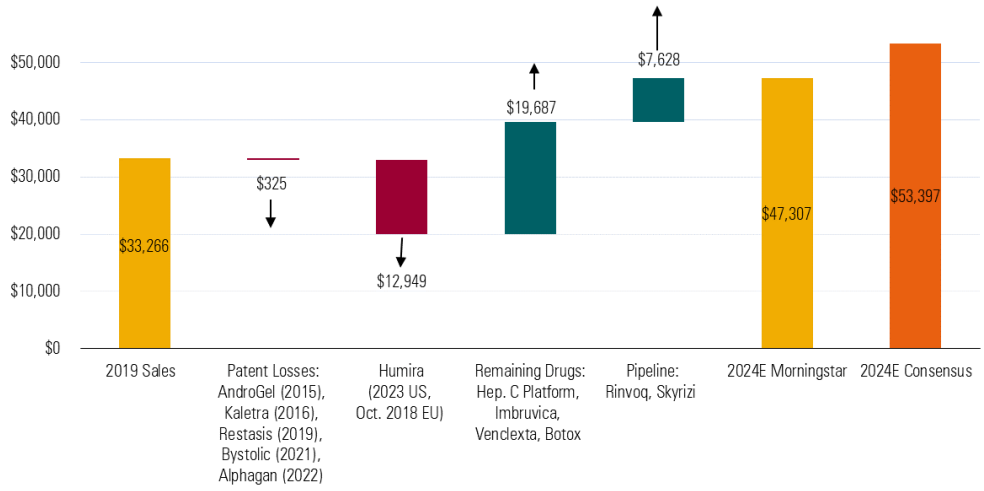
Source: Morningstar, company reports.

Pipeline Reports

AbbVie ABBV

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$97.00	1.02	Medium	Narrow	Negative

Revenue Breakdown USD Millions



Source: Morningstar, company reports, DrugAnalyst/S&P Cap IQ for consensus.

Humira Patent Settlement With Biosimilar Challengers Creates Stronger Outlook

Expiring Patents

AbbVie's biggest challenge over the next five years is the U.S. biosimilar headwind to its key drug Humira, and we expect declines will be much faster than consensus. The majority of biosimilar players have signed settlements for U.S. Humira launches, and we believe Humira sales are safe until 2023 when staggered biosimilars will launch.

Inline Products

Blood cancer drugs Imbruvica and Venclexta are poised for continued gains in chronic lymphocytic leukemia with additional indications in earlier lines of use as well as competitive threats that look

manageable. While Botox faces new competition, the entrenchment of the drug should enable modest long-term growth.

Pipeline

The core of AbbVie's pipeline is focused on immunology drugs Rinvoq and Skyrizi, both of which have shown excellent data.

Moat and Product Portfolio

Expiring Patents

Product:		Humira
Composition:		biologic (monoclonal TNF antibody)
Economics:		7.5% royalty payments (ended by 2019)
Therapeutic Area:		immunology
Patents/Generic Threats:		Dec. 2016 U.S./October 2018 EU
2024 Sales	Morningstar	$6.2 billion
	Consensus	$9.8 billion
Market Model:		psoriasis (p.166), RA (p.167), Crohn's/UC (p.168)

While both branded (IL-17, IL-23, JAKs, S1P1s, Integrins) and biosimilar threats loom, AbbVie's favorable settlement with Amgen and other biosimilar competitors has delayed our projections for a U.S. Humira biosimilar launch until 2023, although European biosimilars launched in October 2018. However, AbbVie still receives an undisclosed royalty on biosimilar Humira sales, which we estimate to be close to 7%.

Product:		Restasis
Composition:		Ciclosporin
Economics:		
Therapeutic Area:		Dry Eye
Patents/Generic Threats:		Weaker patents go to 2024
2024 Sales	Morningstar	$40 million
	Consensus	$100 million
Market Model:		

Restasis is one of the few drugs used for dry eye disease. However, we expect generic competition to erode sales quickly.

Inline Products

Product:		Linzess
Composition:		small molecule (Guanylate cyclase-C agonist)
Economics:		
Therapeutic Area:		Irritable bowel syndrome
Patents/Generic Threats:		2026 U.S.
2024 Sales	Morningstar	$927 million
	Consensus	$947 million
Market Model:		

Linzess treats irritable bowel syndrome with constipation and chronic idiopathic constipation. We expect generics in 2026, but they could come earlier if the 2026 method-of-use patent doesn't hold.

Inline Products (continued)

Product:		Imbruvica
Composition:		small molecule (BTK)
Economics:		50% of profits to J&J
Therapeutic Area:		hematological oncology CLL: Chronic lymphocytic leukemia FL: Follicular lymphoma
Patents/Generic Threats:		Nov. 2027 U.S.(assumes Hatch Waxman Patent Term Extension)/Oct. 2026-29 Europe
2024 Sales	Morningstar	$7,096 million
	Consensus	$7,775 million
Market Model:		CLL (p.187), NHL (p.185), multiple myeloma (p.188)

Imbruvica is approved for several indications, including mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, relapsed/refractory marginal zone lymphoma, and refractory chronic graft-versus-host disease (cGVHD). We believe that with an 84% reduction of death as compared with chlorambucil in first-line CLL, Imbruvica is well positioned to take share in CLL. AbbVie expects non-risk-adjusted sales of $11 billion by 2025, which seems high, especially after the drug's failure in Phoenix (non-GCB DLBCL).

However, more share gains in first-line CLL are possible, given the positive data (OS HR of 0.17) from E1912 at ASH 2018 in younger/more fit patients taking Imbruvica plus Rituxan versus chemo plus Rituxan, which was added to the U.S. label in April 2020. Also, positive data from Illuminate (1L CLL less fit) with Gazyva versus chemo plus Gazyva should help in first-line CLL. Share of first-line CLL is 50% in the U.S. (30% starting as first line), so there is room to grow, but total patient share in second-line CLL is close to 75% under treatment, suggesting some saturation. Key upcoming studies include Selene in RR FL (2020), but early-stage data in FL looked poor. Also, the drug did fail in Resolve (pancreatic cancer).

The biggest competitive threat in CLL is from Astra's BTK Calquence, which posted progression free survival (PFS) improvements of 69% (refractory mono versus Rituxan plus idelalisib or Rituxan plus bendamustine) and 90% (first line combined with Gazyva versus Gazyva plus chlorambucil). Imbruvica posted PFS improvements of 78% (refractory versus Arzerra) and 77% (first line combined with Gazyva versus Gazyva plus chlorambucil). Safety looks slightly better with Calquence, which had serious adverse rates of 39% versus 58% for Imbruvica in the first-line setting with atrial fibrillation a key outlier (3% versus 12% for Imbruvica), but headache and bleeding rates were better for Imbruvica. A head to head study versus Calquence should report out in March 2021 in the refractory CLL patient group.

One other threat is from Beigene's Brukinsa (already approved for mantle cell lymphoma), which should have a head to head Phase 3 study versus Imbruvica report out in early 2021 in refractory CLL.

Inline Products (continued)

Product:		Venclexta/venetoclax (ABT-199)
Composition:		small molecule (Bcl-2 inhibitor)
Economics:		50/50 split with Roche (AbbVie books sales)
Therapeutic Area:		hematological oncology CLL: Chronic lymphocytic leukemia AML: Acute myeloid leukemia FL: Follicular lymphoma
Patents/Generic Threats:		2031 U.S./EU
2024 Sales	Morningstar	$2,906 million
	Consensus	$3,051 million
Market Model:		CLL (p.187), NHL (p.185), multiple myeloma (p.188)

Venclexta was initially approved in a subset of CLL patients with the 17p deletion, but approval was extended in 2018 to relapsed/refractory CLL (higher PFS and OS with Venclexta/Rituxan than with the prior standard of care, Rituxan and bendamustine, in the Murano study) and to first-line CLL in 2019 (Gazyva/ Venclexta combination had a hazard ratio of 0.33, or 67% PFS risk reduction, in the CLL14 study versus Gazyva plus chemo, in patients with co-existing conditions). Venclexta is boxed out of some combinations, like CD20/BTK combos; Gazyva/Imbruvica was approved in a similar setting in January 2019 (illuminate study showed hazard ratio of 0.23 versus Gazyva plus chemo), and Astra's study of competing BTK inhibitor Calquence in Elevate-TN had a similar design and showed a hazard ratio of 0.1. However, we think the fixed 12-month duration of a Venclexta combination is appealing, and AbbVie is also testing a limited duration Imbruvica/Venclexta combination in CLL (versus Gazyva/chemo) with data expected in 2021. CLL combinations could also evolve to include triple combinations (Astra's phase 3 trial of Calquence/Venclexta/Gazyva against Calquence/Venclexta should have data in 2022). Venclexta is also approved in the 50% of first-line AML patients who are unfit for intense chemo, and we expect strong data to make it the standard of care. The Viale-A showed a strong survival benefit with azicitadine at EHA 2020 (14.7 months versus 9.6 months on azacitadine alone), although Pfizer's Daurismo also saw significant survival benefit in BRIGHT 1003, and Venclexta saw an insignificant survival improvement in confirmatory AML study Viale-C in March 2020. We see potential sales approaching $1 billion in this indication, and studies in RR AML in combination with idasanutlin had efficacy better than either drug alone. In addition, early data in MDS hint that Venclexta combination with azacitadine could improve on azacitadine alone. Phase 3 data from the Bellini study (with Velcade) in 2019 in multiple myeloma showed strong progression-free survival benefit, but higher proportion of deaths in the Venclexta arm limits potential in overall MM market; the Canova trial (with dexamethasone) continues in the 20% of patients with t(11;14) positive disease and should have data in 2021. Early-stage studies are in progress in lymphoma (with Polivy and Gazyva or Rituxan). Overall, we see 70% of Venclexta's 2024 sales coming from CLL, and we see the CLL market growing to $11 billion by 2024.

Product:		Mavyret: ABT-530 (pibrentasvir)/ABT-493 (glecaprevir)
Composition:		small molecule (NS5A, NS3/4a PI)
Economics:		Double-digit royalty to Enanta on ABT-493 (50% of this drug)
Therapeutic Area:		hepatitis C
Patent:		2029-32
2024 Sales	Morningstar	$1,844 million
	Consensus	$1,506 million
Market Model:		HCV (Page 192)

The drug is very competitive (and likely a little better on the margin) with Gilead's Harvoni and Epclusa due to the 98% efficacy with the eight-week regimen across genotypes. Overall, we expect AbbVie's drug will grow from 45% of the hepatitis C market to more than 55% in 10 years. However, the market is shrinking given the curative nature of the drug treatments. Additionally, the decision to exclude the drug from Express Scripts' formulary in 2020 could weigh on growth. CVS had already excluded the drug in 2019.

Inline Products (continued)

Product:		Orilissa/Elagolix
Composition:		Small-molecule gonadotropin antagonist
Economics:		Double-digit royalty to Neurocrine
Therapeutic Area:		endometriosis/uterine fibroids
Patent:		2029 (targeting U.S. and Canada)
2024 Sales	Morningstar	$722 million
	Consensus	$911 million
Market Model:		—

The endometriosis market (chronic pelvic pain throughout the menstrual cycle) is large with 17 million women worldwide (1.5 million seek treatment, but current treatments cause hot flashes and bone-density changes). In phase 3 studies Violet and Solstice, the drug reduced pain by 40% (low dose) and 75% (high dose) versus placebo of 20%, but side effects of a 2.5% reduction in bone mineral density at the high dose (3.2% for Lupron as reference) are concerning. The uterine fibroids indication could be much bigger, as 19 million people have uterine fibroids and surgery is the only current option. Elagolix with Activella outperformed placebo by 50% in reducing bleeding, with no impact on bone mineral density. We expect a 2020 launch for uterine fibroids (FDA approved in May 2020 as Oriahnn). The drug is priced close to $10,000, in ICER's acceptable range. Other competitive drugs with the same mechanism of action include Myovant's phase 3 drug relugolix (similar, slightly less effective in Phase III but maybe safer on bone side effects, approval likely in late 2020 and this drug is also being studied for prostate cancer) and ObsEva's drug linzagolix (potentially best in class efficacy from Phase III studies and likely approval in late 2020). We are most concerned about linzagolix's strong efficacy (94% response rate versus 69-76% for Orilissa).

Product:		Skyrizi/Risankizumab
Composition:		biologic (IL23 antibody)
Economics:		undisclosed royalties to Boehringer Ingelheim
Therapeutic Area:		immunology
Patent:		April 2033
2024 Sales	Morningstar	$3,197 million
	Consensus	$3,681 million
Market Model:		psoriasis (p.166), Crohn's/UC (p.168)

Skyrizi gained approval in 2019 (U.S. April, EU and Japan March). Phase 3 data in moderate to severe psoriasis patients showed PASI 90 at 16 weeks of 72%-75% of patients versus 42%-48% for Stelara and Humira. Safety looks good, but six deaths in the Skyrizi arms potentially due to cardiovascular reasons is concerning. This drug will be the third IL23 to the market, partially limiting its potential. However, head-to-head data versus Cosentyx (IL-17) showed Skyrizi to be statistically significantly better on the primary endpoint of PASI 90 (87% versus 57%) with similar side effects (5.5% serious adverse events and 1.2% dropouts versus 3.7% and 4.9%, respectively).

Phase 3 studies are ongoing in several more indications. The expected approval dates are as follows: psoriatic arthritis 2022, Crohn's 2022, atopic dermatitis 2023, and ulcerative colitis 2024, with phase III data generally coming a year before approval. In psoriatic arthritis, the efficacy data looks similar to or slightly worse than other biologics. In Crohn's, Skyrizi looks as good if not better than Stelara (a leader in Crohn's) with efficacy rates ranging from 14-20% versus 14% for Stelara.

Product:		Rinvoq/Upadacitinib
Composition:		small molecule (JAK1)
Economics:		—
Therapeutic Area:		immunology/RA (rheumatoid arthritis)
Patent		U.S. 2033/EU2034
2024 Sales	Morningstar	$2,992 million
	Consensus	$2,957 million
Market Model:		RA (p.167), atopic dermatitis (p.164)

The drug was approved in August 2019 (U.S.) and in December 2019 (Europe). While the RA space is getting increasingly crowded, the drug's potentially leading efficacy in RA and potential in other immunology indications should drive peak sales close to $3 billion. Phase 3 data in biologic and DMARD refractory patients showed an ACR 70 rate of low 20s versus midteens for Eli Lilly's baricitinib (not head-to-head studies).

Head to head data versus Dupixent in atopic dermatitis should read out in 1Q21. The expected approval dates for new indications are as follows: psoriatic arthritis 2021 (filed with FDA and EMEA in June 2020), atopic dermatitis 2021, ankylosing spondylitis 2021, ulcerative colitis 2023, Crohn's 2023, and Axial Spa 2023. (Phase III data is generally expected about a year ahead of the approval dates.) In Crohn's, Rinvoq has shown efficacy rates of 21% versus 14% for Stelara (a leader in the class). In atopic dermatitis, Rinvoq looked similar to Dupixent (market leader) at the 15mg dose (approved dose for RA) on the EASI75 metric.

Inline Products (continued)

Product:		Botox Cosmetic
Composition:		Botulinum toxin
Economics:		
Therapeutic Area:		Wrinkle remover
Patent:		Largely expired
2024 Sales	Morningstar	$4,206 million total (50% cosmetic/50% therapeutic)
	Consensus	$4,816 million total
Market Model:		

Botox's cosmetic business represents close to 40% of total Botox sales, and the launch of Jeveau (from Evolus in 2019), Botulax (from Hugel in 2020 potentially), and RT002 (from Revance in 2020 potentially) represents new competition into a market in the U.S. which previously had only three players—Allergan's Botox, Galderma's Dysport, and Merz's Xeomin. Allergan continues to dominate this market with nearly 70% share, and even though we expect modest market share losses to new competition, we still anticipate positive growth for Botox. Physician familiarity with technique, injection differences between products, customer and physician loyalty programs for Allergan's broad aesthetics, and limited training resources are just some of the reasons we think this remains a high-barrier-to-entry market. Additionally, Evolus' current CEO David Moatazedi—former senior vice president and head of the U.S. medical aesthetics division at Allergan, has said that he doesn't want to commoditize the market and doesn't plan on competing on price. Similarly, Revance's management says that it views its toxin as a premium product given its potential differentiation.

Of the new competition, Revance's RT002 seems better positioned because of its differentiation as the first neurotoxin with a longer duration effect. Regardless, we still anticipate limited market share gains for Revance since the duration effect doesn't appear dramatically different from compounds like Botox. Revance's Phase 3 SAKURA results suggest about a six-month duration effect based on 35% and 29% patient response rates for none to mild facial wrinkle severity (investigator assessed) by week 24 in SAKURA I and 2, respectively. The same measures by patient assessment were lower at 24% and 22%, respectively. Botox had a similar response rate by week 17 in its Phase 3 trials, implying RT002 has between a one- and two-month benefit. In our opinion, Revance's results are not dramatically different from most current neuromodulators, including Botox, that generally have a three- to five-month duration effect with more frequent injections seeming to extend the duration effect to the higher end of the range. We imagine the duration effect for Revance might therefore not be enough to switch many users who have a long history of adequate wrinkle control with Botox. Additionally, Revance will face challenges like smaller neurotoxin players of having a limited aesthetics portfolio as well as marketing and training constraints, including in international markets. We'd likely grow more concerned about Botox's future if a major aesthetics competitor like Johnson & Johnson bought Revance.

Product:		Botox Therapeutic
Composition:		Botulinum toxin
Economics:		
Therapeutic Area:		Several (migraine, overactive bladder, and smaller indications)
Patent:		Largely expired

Botox carries a leading number of therapeutic indications (8 indications, including migraine and overactive bladder), well ahead of other approved neurotoxins which carry about half of this amount of indications. However, in migraine (40% of the therapeutic sales), competition is emerging outside of neurotoxins from new CGRP drugs.

Product:		Juvederm
Composition:		Soft tissue filler
Economics:		
Therapeutic Area:		Facial filler
Patent:		Potentially lasting to 2021-2026
2024 Sales	Morningstar	$1,114 million
	Consensus	$810 million
Market Model:		—

Juvederm's collection of facial fillers looks competitive versus Restylane, Sculptra, and Radiesse. One advantage of Juvederm is it uses hyaluronic acid, which is a naturally occurring sugar found in the body, which may mean less Juvederm is needed as the injection can lead to the body creating more of the sugar naturally. Restylane is also hyaluronic acid.

Inline Products (continued)

Product:		Ubrelvy
Composition:		Small molecule (CGRP)
Economics:		
Therapeutic Area:		Acute migraine
Patent:		
2024 Sales	Morningstar	$300 million
	Consensus	
Market Model:		migraine (p. 178)

Approved in December 2019, Ubrelvy is the first oral CGRP to market and the first CGRP approved for acute use. Liver toxicity ended development of earlier oral CGRPs, but ubrogepant passed two liver safety studies in healthy volunteers in October 2018, and the drug was approved with no black box warning. We expect AbbVie's migraine entrenchment with Botox could help uptake, and ICER's price benchmark of $4,200-$4,600 is quite close to the $4,900 list price.

Product:		Vraylar
Composition:		Small molecule (D3 and D2 receptor agonists)
Economics:		
Therapeutic Area:		CNS, bipolar depression, schizophrenia
Patent:		Mar. 2027
2024 Sales	Morningstar	$1,527 million
	Consensus	$1,544 million
Market Model:		—

While in a crowded field of generic and branded drugs, Vraylar has a slightly different mechanism of action than the traditional antipsychotics. The differentiation can support use in refractory patients or patients with heavy side effects from other drugs.

Moat Trend and Product Pipeline

Product:		Veliparib (ABT-888)
Composition:		small molecule (PARP)
Economics:		—
Therapeutic Area:		cancer
Launch Year/Probability:		2020/50%
2024 Sales	Morningstar	$276 million
	Consensus	$138 million
Market Model:		—

Veliparib missed its primary endpoints in two clinical phase 3 trials, one for non-small-cell lung cancer and the other for triple-negative breast cancer. Also, data in subsequent breast and ovarian cancer trials doesn't look competitive, so our outlook for the drug is fairly low and AbbVie management has guided to peak sales approaching $400 million, which seems reasonable.

Product:		Atogepant
Composition:		small molecule/oral CGRP
Economics:		
Therapeutic Area:		migraine
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	$313 million
	Consensus	$276 million
Market Model:		migraine (p. 178)

Atogepant's phase 2b/3 results showed a 3.55 to 4.14 reduction in headache days across all dosage forms (statistically significant) versus 2.85 for placebo. This efficacy looks similar to the biologic CGRP drugs already launched. While liver side effects have hurt other oral CRGP drugs, atogepant liver side effects look manageable. Phase III data should report out in 2020 and 2021, supporting a potential filing in 2022.

Moat Trend and Product Pipeline (continued)

Product:		ABBV-3373
Composition:		Biologic (TNF/GRM antibody drug conjugate)
Economics:		
Therapeutic Area:		Rheumatoid arthritis
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	--
Market Model:		RA (p. 167)

ABBV-3373 is an investigational anti-tumor necrosis factor (TNF) Glucocorticoid Receptor Modulator (GRM) steroid antibody drug conjugate (ADC) that showed solid phase 2a results that look better than what Humira has shown on efficacy from a historical perspective.

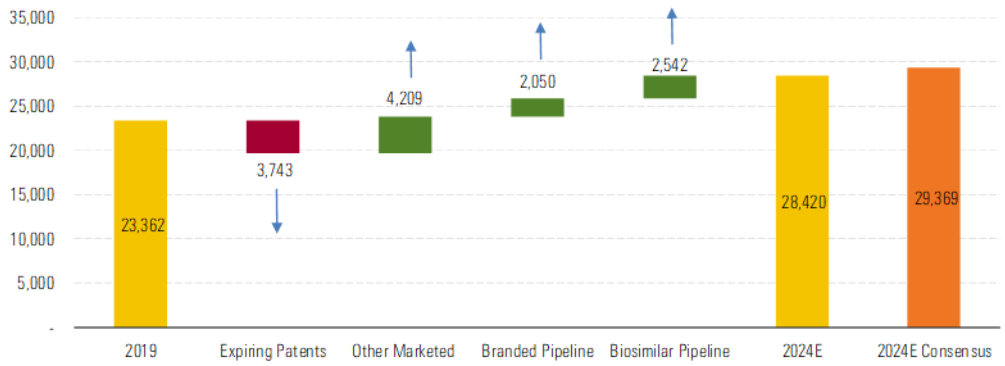
Product:		Abicipar pegol
Composition:		Biologic (DARPin technology)
Economics:		
Therapeutic Area:		Wet age-related macular degeneration
Launch Year/Probability:		2024/20%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	--
Market Model:		

Abicipar pegol received a complete response in June 2020 due to the high inflammation rates suggesting an unfavorable risk/reward for treatment. While AbbVie plans to continue to work with the FDA to bring the drug to the market, the prospects look poor.

Amgen AMGN

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★	$219.00	1.17	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports; DrugAnalyst, Visible Alpha for consensus.

Repatha Acceleration, Oncology Pipeline Progress Needed to Counter Biosimilar, Enbrel Pressure

Expiring Patents

Biosimilar Neulasta and generic Sensipar were a $2.5 billion top-line headwind in 2019, and we expect an additional $3.7 billion headwind over the next five years from these therapies and Amgen's aging anemia franchise (Epogen and Aranesp). Coherus and Mylan biosimilar versions of Neulasta launched in the U.S. in 2019, with Novartis entering in 2020 and continuing rapid double-digit declines. Pfizer's Epogen biosimilar and contractual price adjustments should weigh on Epogen and Aranesp sales. Sensipar's U.S. hit is largely behind Amgen, with European generic pressure coming in 2020.

Inline Products

Demand for Prolia and Xgeva continues to grow and helps support Amgen's wide, stable moat. However, branded competition is weighing on our below-consensus estimates for Enbrel (immunology), Kyprolis (multiple myeloma) and Aimovig (migraine). We remain above consensus on cholesterol drug Repatha; treating patients uncontrolled by statins at recently lowered list prices should allow for sales to peak at $2.5 billion ahead of cardiovascular outcomes data from Novartis' inclisiran (2022). Amgen's in-house biosimilar pipeline is beginning to launch, starting with biosimilar versions of AbbVie's Humira and Roche's Herceptin and Avastin, and we assume $3.1 billion in Amgen biosimilar sales in 2024.

Pipeline

Amgen's pipeline could see significant catalysts in the second half of 2020, including phase 3 data for asthma drug tezepelumab and heart failure drug omecamtiv, pivotal phase 2 lung cancer data for AMG

510, and initial data for half-life extended bispecifics like AMG 701 (multiple myeloma), AMG 757 (SCLC) and AMG 160 (prostate cancer).

Moat and Product Portfolio

Expiring Patents

Product:		Epogen
Composition:		biologic (recombinant erythropoietin protein)
Economics:		U.S. rights (J&J excluding U.S.)
Therapeutic Area:		nephrology (anemia)
Patents/Generic Threats:		2015 U.S.
2024 Sales:	Morningstar	$400 million
	Consensus	$350 million
Market Model:		—

Epogen declines should continue due to dialysis drug bundle rebasing, competition from branded Mircera, Amgen's strategic shift of dialysis patients to Aranesp, step downs in pricing in the DaVita contract (through October 2022), and biosimilars. After two complete response letters, Pfizer has finally received FDA approval for its biosimilar, Retacrit, which launched in November 2018 at a roughly 30% discount to Amgen's list price and 10% discount to net (ASP) price. Retacrit held 20% of the market by the end of 2019. Step therapy in Medicare Advantage started in 2019 and is likely boosting biosimilar launches, but UnitedHealth is not subjecting Epogen to step therapy (we assume due to steep enough branded Epogen discounts). New, potentially more effective oral anemia drugs include Astra and FibroGen's roxadustat, which beat Epogen in a dialysis trial (FDA approval Dec 2020E), and Akebia's vadadustat, which was filed in Japan in 2019 and is in a global phase 3 program. However, complex reimbursement through CMS makes their viability less certain.

Product:		Neulasta
Composition:		biologic (pegylated recombinant G-CSF protein)
Economics:		—
Therapeutic Area:		oncology (neutropenia)
Patents/Generic Threats:		2015 U.S./2017 EU
2024 Sales:	Morningstar	$1.3 billion
	Consensus	$1.2 billion
Market Model:		—

Despite initial delays in biosimilar approvals, Amgen is now facing multiple biosimilar competitors that should lead to extended double-digit sales declines. Novartis, Apotex, and Coherus all received complete response letters from the FDA in 2017, as it proved difficult to show biosimilarity to Neulasta, partly due to immunogenicity concerns. However, two biosimilars were approved in 2018; Mylan's Fulphila (launched summer 2018) and Coherus' Udenyca (launched January 2019). Novartis' Ziextenzo was approved in November 2019, followed by Pfizer's Nyvepria in June 2020. Competition was in full swing starting in 2019, and certain settings (such as 340B hospitals, where biosimilars have a reimbursement advantage) appear more vulnerable than others. Launch prices for Fulphilia and Udenyca were roughly 33% lower than Neulasta's list price, and Ziextenzo is launching at a 37% discount to list price, but these translate only slightly lower than Neulasta's net price. We expect prices to go lower as the drugs compete for contracts, and uptake to be helped by the rapid turnover of patients in this setting relative to the chronic market for Remicade, which has seen more limited share loss, albeit with significant price concessions. Changes to Medicare Advantage (a third of Medicare Part B) in 2019 allowing plans to push patients to step through cheaper options first could also boost biosimilar uptake. Amgen's Onpro kit, a timed-release patch that allows patients to avoid a post-chemo visit to begin Neulasta treatment, represented 54% of the U.S. long-acting neutropenia market at the end of first-quarter 2020, with Amgen holding on to roughly 72% share of the market overall, despite biosimilar competition. "Biobetter" competition in Europe from Teva's Lonquex has competed with international sales of Neulasta since 2013, but several direct Neulasta biosimilars (from firms including Coherus, Apotex, and Novartis) have recently been approved in Europe, although Amgen's international Neulasta sales are a much smaller portion of the global Neulasta franchise than U.S. sales.

Expiring Patents (continued)

Product:		Aranesp
Composition:		biologic (pegylated recombinant erythropoietin protein)
Economics:		—
Therapeutic Area:		nephrology/oncology (anemia)
Patents/Generic Threats:		2024 U.S./2016 EU
2024 Sales:	Morningstar	$1 billion
	Consensus	$1.2 billion
Market Model:		—

Aranesp nephrology sales (about two-thirds of total sales) are vulnerable to branded competition like Mircera and potential new entrants like Astra's roxadustat (proved non-inferior to Aranesp in non-dialysis CKD patients in June 2020) and Akebia's vadadustat, as well as biosimilar Epogen (Pfizer's Retacrit was launched in the U.S. in November 2018). Aranesp's oncology sales (one-third of total sales) are mostly vulnerable to Retacrit competition, as the biosimilar has a broad label in nephrology and oncology. Amgen did transition some dialysis patients to Aranesp from Epogen a few years ago, and 80,000 dialysis patients were taking Aranesp in the U.S. in 2016, providing some defense against direct biosimilar competition. We don't have any direct biosimilar threats on our radar. Step therapy in Medicare Advantage (starting 2019) and favorable reimbursement through the Medicare 340B reimbursement program could boost biosimilar launches, as UnitedHealth is subjecting Aranesp to step therapy (but only for new patients).

Inline Products

Product:		Repatha (evolocumab)
Composition:		biologic (PCSK9 antibody)
Economics:		—
Therapeutic Area:		cholesterol
Patents/Generic Threats:		2029 U.S./EU
2024 Sales:	Morningstar	$2.5 billion
	Consensus	$1.8 billion
Market Model:		—

We expect this will be a $2.5 billion peak sales opportunity for Amgen, as strong growth in the near term due to solid efficacy and better pricing will likely plateau by the middle of the decade. Novartis/Medicines Company's twice-yearly inclisiran, which looks like a strong competitor (Repatha is every two weeks or monthly), is likely launching in late 2020, with cardiovascular outcomes data in 2022 that could weigh on Repatha's growth. Esperion's cheaper but less potent oral ACL inhibitor Nexletol/bempedoic acid and ezetimibe combination drug Nexlizet (both approved Feb 2020, priced at roughly $3,700 a year, CV outcomes data 2022E) could also compete, as they have shown LDL lowering of 18% and 38%, respectively. Sanofi and Regeneron's Praluent and Amgen's Repatha both received FDA approval in 2015 to slow initial uptake, as the majority of prescriptions were not successfully filled (due to high hurdles for qualifying for coverage from payers) and high out-of-pocket costs in the Medicare setting (where patient assistance isn't allowed). While Praluent became the exclusive PCSK9 for Express Scripts' national formulary in 2018, with a price tied to ICER's cost-effectiveness analysis, we're encouraged by Amgen's agreements with payers like CVS and Anthem, and Repatha is back on the Express Scripts formulary for 2020. Amgen also introduced a new National Drug Code for Repatha in October 2018 at a 60% lower price, which should help more patients with prescriptions afford the significant out of pocket costs, particularly in Medicare, where patient assistance programs aren't allowed. The roughly $6,000 price for this new Repatha code fits well with our previous assumptions on net pricing in this competitive market. The clinical significance of the 15% risk reduction in Repatha's cardiovascular outcomes trial has been debated, but we think the late 2017 prescribing label update to include risk reduction for heart attacks (27%) and stroke (21%) has pushed payers to open access, particularly given new risk-sharing contracts that likely result in lower net prices. We also expect risk reductions to improve as patients remain on therapy.

Product:		Enbrel
Composition:		biologic (TNF fusion protein) North America rights (PFE ex NA) arthritis/psoriasis
Economics:		—
Therapeutic Area:		—
Patents/Generic Threats:		2028 U.S.
2024 Sales:	Morningstar	$1.7 billion
	Consensus	$3.6 billion
Market Model:		psoriasis (p.166), RA (p.167)

Enbrel grew strongly through 2016 despite shrinking market share, thanks to underlying market growth and double-digit price increases. However, Amgen's ability to raise prices fell in 2017, as newer options (including oral Otezla and high-efficacy injectables like Novartis' Cosentyx and Eli Lilly's Taltz) are gaining share rapidly in dermatology. In addition, Humira biosimilars (2023 U.S. entry) should lead to declines. Novartis' biosimilar Enbrel (Erelzi) was approved in the U.S. in August 2016, but we do not expect it to launch at risk, given the strength of the 2028 composition patent. Novartis appealed a U.S. district court ruling against it (in favor of Amgen) in 2019, with a hearing in March 2020 and a ruling again in favor of Amgen in July 2020 (although Novartis could appeal to the Supreme Court).

Product:		Otezla (apremilast)
Composition:		small molecule (PDE4 inhibitor)
Economics:		—
Therapeutic Area:		psoriasis/psoriatic arthritis
Patents/Generic Threats:		2028 U.S./2028 EU
2024 Sales:	Morningstar	$3 billion
	Consensus	$3.2 billion
Market Model:		psoriasis (p.166)

Launched in 2014, Otezla is seeing strong uptake as a safe oral despite more modest efficacy, and we assume peak sales of more than $3 billion. Our estimates are shy of Amgen's forecast for double-digit growth over the next five years, as we're concerned about competition and pricing, but we do recognize the significant opportunity to expand sales into the mild, post-topical setting (6 million in the U.S., which is the key market opportunity) following positive topline data in May 2020, as well as the scalp psoriasis label expansion in April 2020. Head-to-head data against Bristol's TYK2 (mid-2020) stands as a competitive threat in the moderate to severe oral psoriasis market. Amgen is also studying the drug as a treatment for COVID-19, but we don't incorporate sales here yet, due to lack of data. Amgen acquired global rights to Otezla from Celgene in November 2019 for $13.4 billion, in conjunction with Bristol's acquisition of Celgene. The acquisition fits well with Amgen's U.S. immunology portfolio (largely Enbrel) and helps expand Amgen's immunology reach internationally beyond Amgevita (including in Japan, where it was approved in 2016, and China). The vast majority of Otezla patients (more than 85%) take the drug before taking a biologic treatment, and we think the drug is expanding the market by offering a novel option for patients with more moderate disease. The lack of a black box safety warning on the drug's prescribing label is also reassuring to risk-sensitive dermatologists. The drug treats more than 30% of new U.S. psoriasis patients. Otezla was priced at a 35% discount to the list price of biologic treatment options in 2016, and net prices fell substantially in 2017 in exchange for expanded access in PBM formularies (70 million-100 million more patients are covered who do not need to step through Humira or Enbrel treatment prior to Otezla).

Product:		Prolia
Composition:		biologic (RANKL antibody)
Economics:		—
Therapeutic Area:		osteoporosis
Patents/Generic Threats:		2025 U.S./EU
2024 Sales:	Morningstar	$3.2 billion
	Consensus	$3.4 billion
Market Model:		—

Despite the strong market for generic versions of branded bisphosphonates like Fosamax in osteoporosis, we think rare fracture side effects, poor tolerability, and low compliance rates with these drugs have made Amgen's differentiated antibody Prolia (injected every six months) a popular option. Market penetration and retention have been strong globally. Prolia prevents the resorption of bone, making it complementary to Amgen's bone-forming drug Evenity. In 2019, 4 million patients took Prolia, with steady double-digit volume increases driving sales growth. Amgen expects to launch in China shortly. Novartis has a biosimilar in testing (the Rosalia study) as of mid-2019.

Product:		Evenity/Romosozumab (AMG 785)
Composition:		biologic (sclerostin antibody)
Economics:		50/50 collaboration with UCB. Astellas (Japan)
Therapeutic Area:		osteoporosis
Patents/Generic Threats:		2026 U.S./EU
2024 Sales:	Morningstar	$800 million
	Consensus	$850 million
Market Model:		—

This novel bone-forming product, which showed superiority to Forteo in bone mineral density improvements in the phase 3 Structure trial, looks complementary to Prolia for patients at high risk of fracture, and the initial launch in the U.S. and Japan in 2019 is surpassing our expectations (approved in Europe in December 2019). Evenity was approved in the U.S. in April 2019 for patients at high risk of fracture, and bars women who have had a heart attack or stroke in the past year from treatment (Amgen received a complete response letter back in 2017 tied to cardiovascular concerns). Roughly 2 million women in the U.S. have had a fracture and are at risk for another near-term fracture. In the Frame study, Evenity showed a significant 73% relative risk reduction for vertebral fractures versus placebo, and while the risk of nonvertebral fractures was not significantly lowered, we think this is due to the overall low nonvertebral fracture rate in Latin America (a heavy focus of the trial) and the short length of monitoring (only 12 months). The Arch study showed superior efficacy on fracture risk versus Fosamax (48% lower risk of vertebral fracture, 19% lower risk of nonvertebral fracture) but a higher risk of serious cardiovascular adverse events (2.5% or 50 patients versus 1.9% or 38 patients). We think its once-monthly administration (over a limited 12-month period) is an advantage over Radius Health's once-daily Tymlos (approved April 2017). Pfenex's generic Forteo (approved October 2019) could represent the biggest threat to long-term sales, although Evenity's duration of treatment is shorter (and cheaper) than 18-month Tymlos dosing and two-year Forteo dosing.

Product:		Xgeva
Composition:		biologic (RANKL antibody)
Economics:		BeiGene (China equal profit share)
Therapeutic Area:		prevention of bone mets
Patents/Generic Threats:		2025 U.S./EU
2024 Sales:	Morningstar	$2.8 billion
	Consensus	$2.4 billion
Market Model:		—

Xgeva's differentiation from Zometa has allowed strong growth beyond Zometa's patent expirations in 2013. Xgeva was originally approved to prevent fractures in patients with bone metastases from solid tumors, but the label was updated to include prevention of skeletal-related events in patients with multiple myeloma in January 2018. Amgen's BeiGene collaboration allows BeiGene to launch Xgeva in China, sharing profits equally with Amgen.

Product:		Kyprolis
Composition:		small molecule (proteasome) inhibitor
Economics:		—
Therapeutic Area:		oncology (multiple myeloma)
Patents/Generic Threats:		2027 U.S./2030 EU
2024 Sales:	Morningstar	$1.3 billion
	Consensus	$1.4 billion
Market Model:		multiple myeloma (p.188)

Superiority data to Velcade in the relapsed setting (Endeavor) made Kyprolis a best-in-class proteasome inhibitor, and data in combination with Revlimid in the Aspire trial showed 48-month OS in the relapsed setting (over 40 months on Rev/dex alone) and allowed label expansion in 2018. However, approved combinations such as Darzalex/Revlimid (Pollux study) and Darzalex/Pomalyst represents stiff competition. That said, the Candor study (released at ASH 2019) showed the ability of Kyprolis to combine well with Darzalex in the relapsed setting, which could be added to the label in 2020. We think Kyprolis will continue to grow to $1.5 billion, as duration of therapy for patients increases and as more convenient once-weekly administration is rolled out. While Kyprolis administration (twice-a-week infusions) is less convenient than oral options, recent data from the Arrow study showed that once-weekly dosing is more effective than the standard twice-weekly dosing, with superior PFS, and this was added to the label in October 2018. In the first-line setting, head-to-head data against Velcade (Clarion study) and for a Revlimid combination against a Velcade Revlimid combination (Endurance, ASCO 2020) were both disappointing, giving Velcade more staying power in first-line regimens, particularly as Velcade generics are more widely embraced (the only launched generic is an IV formulation, and Takeda does not expect a subcu competitor in 2020).

Product:		Aimovig/erenumab/AMG 334
Composition:		biologic (CGRP-R antibody)
Economics:		AMGN: U.S./Japan sales, double-digit royalty ROW from Novartis. Novartis: ROW sales, significant U.S. royalty (co-commercialize)
Therapeutic Area:		migraine prophylaxis
Patents/Generic Threats:		2031 U.S./2033 EU
2024 Sales:	Morningstar	$725 million
	Consensus	$900 million
Market Model:		migraine (p.178)

This CGRP receptor antibody appears to prevent migraines in both episodic and chronic migraine settings. However, we remain below consensus on migraine drug Aimovig's U.S. sales potential given the tough competitive landscape. Eli Lilly's Emgality and Teva's Ajovy both received approvals shortly after Amgen's first-in-class FDA approval in May 2018, and the launch trajectory has been slow. We expect free drug (for up to 12 months), patient assistance, and negotiation with payers will make net pricing significantly below the roughly $7,000 annual list price, and oral competition from AbbVie and others could reach the prophylaxis market by 2022 (Eli Lilly's Reyvow and AbbVie's Ubrelvy were also approved as acute treatments in late 2019). Aimovig's once-monthly subcu injection looks more appealing than Lundbeck's IV therapy Vyepti (approved Feb 2020), but potentially not as convenient as Teva's Ajovy (which has a quarterly subcu option). With 10-14 million in the U.S. in need of preventive therapy for migraine, we expect Amgen to see peak U.S. sales north of $1 billion. In the phase 2b chronic migraine study, Aimovig patients saw a 6.6-day reduction from baseline in the number of migraine days per month in the last four weeks of the study, versus a 4.2-day reduction in placebo arm. Amgen has also reported data from two phase 3 episodic migraine studies; Arise showed a 2.9-day reduction in monthly migraine days taking the 70 mg dose after 12 weeks, versus a 1.8-day reduction on placebo, and Strive showed a 3.2-to-3.7-day reduction for 70 mg-140 mg doses, versus a 1.8-day reduction on placebo.

Product:		Parsabiv/etelcalcetide (AMG 416)
Composition:		biologic (CaSR peptide agonist)
Economics:		—
Therapeutic Area:		nephrology (SHPT)
Patents/Generic Threats:		2030 U.S./EU
2024 Sales:	Morningstar	$1 billion
	Consensus	$1.1 billion
Market Model:		—

Amgen received approval for this IV treatment in February 2017 and launched with Part B coverage in January 2018. Parsabiv is outside the dialysis reimbursement bundle as an add-on payment for three years, meaning there could be a price hit in 2021, depending on the incremental step up in payment to dialysis operators at that time. Uptake has been strong as the drug has seen solid incorporation at independent and mid-sized dialysis providers and increased adoption at large dialysis centers (Fresenius and DaVita). We think superior efficacy, better GI tolerability, and potential for better compliance (reduced bill burden and timed with dialysis treatments) allow for extended sales beyond oral Sensipar patent expiration.

Product:		Blincyto (blinatumomab)
Composition:		biologic (CD19/CD3 bi-specific antibody)
Economics:		BeiGene (China rights--equal profit share)
Therapeutic Area:		hematological oncology (ALL, NHL)
Patents/Generic Threats:		2023 U.S./2029 EU
2024 Sales:	Morningstar	$350 million
	Consensus	$450 million
Market Model:		NHL (p. 185)

Neurological toxicity looks on par with CAR-T therapies, but the need for continuous infusion and slightly weaker efficacy make this a less appealing option, now that CAR-T treatments are reaching the market (Novartis' Kymriah was approved in pediatric/young adult ALL in August 2017, and Gilead's KTE-X19 should receive approval in adult ALL in 2021). Midstage data in relapsed/refractory ALL allowed Amgen to file and quickly receive approval in 2014, and Amgen extended this approval to the pediatric setting in 2016. We expect approval in China in adult ALL in 2020. This novel bispecific antibody could have even larger sales potential in DLBCL, an aggressive form of lymphoma, but phase 1 data damped our enthusiasm.

Product:		Imlygic (Talimogene laherparepvec/t-vec)
Composition:		biologic (oncolytic virus)
Economics:		—
Therapeutic Area:		oncology (melanoma)
Patents/Generic Threats:		2025 U.S./2026 EU
2024 Sales:	Morningstar	$250 million
	Consensus	$200 million
Market Model:		—

Imlygic produces a significant durable response rate and was approved in 2015 to treat melanoma patients by injection at the lesion site. However, Imlygic monotherapy lacks an overall survival benefit, and published phase 2 data in combination with Yervoy does not yet show a significant difference from Yervoy alone on PFS or OS. Phase 3 trial Keynote-034 compares an Imlygic/Keytruda combination to Keytruda alone, and data could be available prior to 2022, but Opdivo/Yervoy is the standard to beat (the Imlygic combo has a shot at better safety).

Product:		Amjevita (biosimilar Humira)
Composition:		biologic (TNF antibody)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		NA
2024 Sales:	Morningstar	$750 million
	Consensus	$1.1 billion
Market Model:		—

Amgen's biosimilar version of Humira met endpoints in its phase 3 programs in psoriasis and rheumatoid arthritis, and it received FDA approval in September 2016. Amgen and AbbVie reached a settlement allowing launch in Europe in October 2018 ($4 billion Humira market) and the U.S. ($12 billion Humira market) in January 2023. As of early 2020, Amjevita remained the top biosimilar Humira marketed in Europe. We assume peak Amjevita sales rising north of $1 billion.

Product:		Kanjinti (biosimilar Herceptin/trastuzumab)
Composition:		biologic (HER2 antibody)
Economics:		royalties/milestones to Allergan
Therapeutic Area:		breast cancer
Patents/Generic Threats:		NA
2024 Sales:	Morningstar	$675 million
	Consensus	no estimate
Market Model:		—

Amgen entered the market in Europe among early entrants in 2018 (behind Celltrion/Teva's Herzuma and Samsung/Merck's Ontruzant). In the U.S., the firm had a May 2018 PDUFA date but received a complete response letter; a December 2018 refiling put it on track for a six-month review in the U.S., and the drug was launched in July 2019 following a June approval. Initial U.S. uptake has been strong, and the firm ended the first quarter of 2020 with 27% share of the total trastuzumab market. However, growth beyond 2020 could be more challenging due to the sheer number of other Herceptin biosimilars; Amgen's launch in the U.S. was followed by Mylan's Ogivri in December 2019, Pfizer's Trazimera in Feb 2020, Teva/Celltrion's Herzuma in March 2020, and Samsung/Merck's Ontruzant in April 2020. We assume peak sales around $750 million.

Product:		Mvasi (biosimilar Avastin)
Composition:		biologic (VEGF antibody)
Economics:		royalties/milestones to AbbVie/Allergan
Therapeutic Area:		lung cancer
Patents/Generic Threats:		NA
2024 Sales:	Morningstar	$660 million
	Consensus	$360 million
Market Model:		—

Amgen launched Mvasi in July 2019 in the U.S., and we expect it to launch in 2020 in Europe. Mvasi met key endpoints in the phase 3 lung cancer study in 2015. While Avastin's lung cancer sales are falling as PD-1/L1 therapies become more established, we think Mvasi (the first-to-market Avastin biosimilar) is poised to gain nearly $700 million in global sales in the long run. The initial U.S. launch is going strongly, with 33% share of the total bevacizumab market as of the end of first-quarter 2020.

Product:		Avsola/biosimilar Remicade (ABP 710)
Composition:		biologic (TNF-alpha antibody)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		NA
2024 Sales:	Morningstar	$225 million
	Consensus	$275 million
Market Model:		—

Amgen generated positive phase 3 data in June 2018 and gained FDA approval in December 2019, but the firm withdrew its European filing in June 2019, limiting potential sales. In addition, with several products already launched in Europe and two Remicade biosimilars only making slow traction in the U.S., we think this is one of Amgen's smaller opportunities ($250 million peak sales), despite J&J's remaining $3 billion U.S. Remicade franchise (2019 sales).

Moat Trend and Product Pipeline

Product:		biosimilar Rituxan (ABP 798)
Composition:		biologic (CD20 antibody)
Economics:		royalties/milestones to Allergan
Therapeutic Area:		RA/lymphoma
Launch Year/Probability:		2020/100%
2024 Sales:	Morningstar	$300 million
	Consensus	$150 million
Market Model:		—

Following positive data from the Jasmine study in follicular lymphoma in 2019 and a phase 3 study in rheumatoid arthritis completed in 2018, Amgen filed for FDA approval of this Rituxan biosimilar in December 2019, with approval expected by Dec 2020. While Rituxan is a large opportunity--branded sales peaked above $7 billion globally ahead of biosimilar entry in Europe in 2017--Amgen is well behind other biosimilars, including Novartis, Teva, and Pfizer.

Product:		Sotorasib/AMG 510
Composition:		Small molecule (KRAS G12C)
Economics:		—
Therapeutic Area:		Oncology (NSCLC, CRC)
Launch Year/Probability:		2021/30%
2024 Sales:	Morningstar	$400 million
	Consensus	$600 million
Market Model:		—

We model nearly $1 billion in probability-weighted sales by year 10 of our forecast for sotorasib, largely based on its potential in lung cancer, despite competition. Amgen's KRAS inhibitor targets KRAS G12C, which is found in 13% of non-small-cell lung cancer cases and 3%-5% of colorectal cancers. AMG 510 should have key data from a pivotal phase 2 monotherapy study in NSCLC in 2020, as well as phase 1 combo data with Keytruda. Amgen started phase 3 study CodeBreak 200 in May 2020 to verify sotorasib's activity in lung cancer against docetaxel in May 2020. Monotherapy data in colorectal cancer and other solid tumors from the phase 1/2 CodeBreak 100 study at ASCO 2020 (12% ORR, median PFS of 4.2 months) looked relatively weak, although phase 2 monotherapy and phase 1 combination studies with MEK in CRC and lung cancer are ongoing. Amgen is working with diagnostic firms on companion diagnostics, including Guardant Health (liquid biopsy) and Qiagen (tissue-based). AMG 510 had impressive data in lung cancer in 2019, with 54% of patients (seven of 13) seeing a response to treatment, and the drug's strong safety profile makes it a good candidate for combination therapy. The competitive landscape could become crowded behind Amgen; data for Mirati's KRAS-G12C targeting therapy MRTX849 in late 2019 looked similar to AMG 510's data, as 3 of 6 lung cancer patients responded, and the drug is also being tested in combination with Novartis's SHP2 inhibitor TNO155 in G12C mutation patients. Merck/Moderna entered a phase 1 trial in June 2019 with Keytruda and KRAS therapy mRNA-5671, which could have broader efficacy in more KRAS mutant patients. Boehringer moved SOS1 drug BI1701963 into development in KRAS mutation patients in October 2019, and Bayer's SOS1 therapy BAY-293 is entering development. Navire Pharma (IACS-13909) and Novartis (TNO155) are separately targeting SHP2.

Product:		tezepelumab
Composition:		biologic (TSLP antibody)
Economics:		split ~ 60/40, Amgen/Astra
Therapeutic Area:		severe asthma, atopic dermatitis, COPD
Launch Year/Probability:		2021/50%
2024 Sales:	Morningstar	$650 million
	Consensus	$600 million
Market Model:		biologic respiratory (p.171)

Tezepelumab is currently in phase 3 studies in severe uncontrolled asthma and steroid-dependent asthma (data expected late 2020), and if approved, we expect it could see a leading share in the severe asthma setting, where 2 million patients in major markets are uncontrolled and only 15% receive a biologic. TSLP is an upstream driver of airway inflammation. In the phase 2b Pathway study, tezepelumab showed excellent efficacy and safety in patients uncontrolled on inhaled corticosteroids and LABA, with significant 61%-71% reductions in asthma exacerbation rates versus placebo at various doses at 52 weeks. The drug appears to impact IL-4, IL-5, and IL-13 pathways. The reductions were significant regardless of subpopulation, and the study included both high and low eosinophil count patients, which should differentiate the drug from IL-5 antibodies like Astra's Fasenra and Glaxo's Nucala, where only 50% of patients—those with high eosinophil counts—are eligible. Dupixent looks like the key competitor, as it recently received a wider approval in asthma patient dependent on steroid treatment. While tezepelumab failed in a phase 2 atopic dermatitis study, Amgen and Astra initiated another study in this indication in 2019, with data expected in 2021. A phase 2 study in COPD was also started in 2019 (data 2022E). Patents run through 2029 in the U.S. and 2028 in Europe.

Product:		omecamtiv mecarbil (AMG 423)
Composition:		small molecule (cardiac myosin activator)
Economics:		collaboration with Cytokinetics in U.S. (Servier has ex U.S. rights)
Therapeutic Area:		chronic heart failure and left ventricular systolic dysfunction
Launch Year/Probability:		2021/30%
2024 Sales:	Morningstar	$400 million
	Consensus	$500 million
Market Model:		—

This novel compound had been stuck in phase 2 of development for years, as an IV formulation failed in phase 2 in 2013 but positive data from the Cosmic-HF study in 2015 for the oral formulation led to the 2016 decision to move forward into phase 3 trials. Cosmic-HF updates at AHA 2019 confirmed contractility benefit (systolic function) and neutral measures on diastolic function (ability for heart to relax). The drug passed a second interim analysis in Feb 2020, and an independent committee recommended continuing the trial, as futility and superiority analysis did not warrant stopping the trial early. Data from GALACTIC-HF is expected in the fourth quarter of 2020. There are 23 million people worldwide with heart failure and half with reduced left ventricular function, making this a blockbuster market, if approved. Patents run through 2027 in the U.S. and 2025 in Europe.

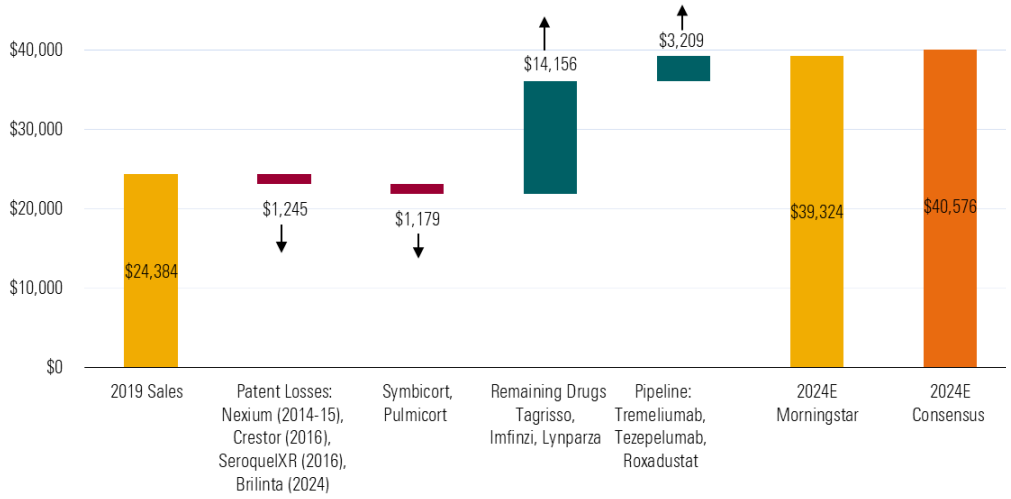
Product:		AMG 420/AMG 701
Composition:		bispecific, BiTE (BCMA)
Economics:		—
Therapeutic Area:		multiple myeloma
Launch Year/Probability:		2022/30%
2024 Sales:	Morningstar	$500 million
	Consensus	$100 million
Market Model:		multiple myeloma (p.188)

Burdensome administration for AMG 420 puts Amgen's hopes for competing in a potentially lucrative BCMA market in multiple myeloma squarely on once-weekly, extended half-life bispecific AMG 701, with the first data (dose escalation data) expected in the second half of 2020. Amgen's phase 1 BCMA-targeted bispecific T-cell engager AMG 420 has had solid data. At a data update at ASCO 2019, AMG 420 maintained a 70% response rate at the chosen 400 ug dose level (10 patients), but improved the MRD-negative complete response rate to 50%. AMG 420's burdensome administration (four-week continuous infusion) and side effect profile tied to its administration (high rate of serious infections) should prevent it from becoming a viable treatment, however. If AMG 701 data are consistent with AMG 420's, we think this could be a strong treatment option, particularly among sicker patients who are ineligible for transplant, although other bispecifics targeting BCMA are in development, including J&J/Genmab's teclistamab and Regeneron's REGN-5458, which have each generated promising early phase 1 data. We assume the efficacy of CAR-T options like Bristol's ide-cel (filed in 2020) and J&J/Legend's JNJ-4528 (filing in 2020) will remain higher and make CAR-T a better option for healthier patients. Preclinical AMG 701 data at ASH 2019 indicate solid efficacy and improved efficacy with Revlimid combination treatment.

AstraZeneca AZN

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$55.00	0.98	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports; DrugAnalyst/S&P Cap IQ for consensus.

Strong Cancer Drug Sales with Inline Products Sets Up Strong Sales Potential

Expiring Patents

With the majority of Astra's patent losses behind the firm and subsiding one-time sales of assets (that Astra has used to bridge itself to strong drug sales in the past), the firm is set up for steady top-line growth.

Inline Products

Tagrisso (strong pricing power in the first-line setting for EGFR lung cancer and adjuvant treatment with limited competition) and Imfinzi (strong positioning in stage 3 lung cancer and small cell lung cancer) should each add over $3 billion in incremental sales over the next five years. Also, a new indication for Fasenra should propel growth, offsetting likely continued weakness from the respiratory franchise.

Pipeline

With several recent approvals, Astra's late-stage pipeline is thinning a bit. However, asthma drug tezepelumab and anemia drug roxadustat looks like the most interesting drugs, each holding peak potential in annual sales over $1 billion.

Moat and Product Portfolio

Expiring Patents

Product:		Crestor
Composition:		small molecule (statin)
Economics:		—
Therapeutic Area:		cardiovascular/cholesterol
Patents/Generic Threats:		2016 U.S./2017 Europe, Japan/2012 Canada
2024 Sales	Morningstar	$649 million
	Consensus	$875 million
Market Model:		—

Generic competition to Crestor quickly eroded sales in the U.S. in 2017 and Europe in 2018 as generic competition grew. Crestor's emerging-market sales should be more stable as brand power is more important in those geographies. Nevertheless, the increasing pricing pressure on off-patent drugs in China is concerning, and volume-based pricing declines led to a 15% decline in total emerging market sales in 1Q20.

Product:		Nexium
Composition:		small molecule (proton pump inhibitor)
Economics:		—
Therapeutic Area:		acid reflux/stomach ulcer
Patents/Generic Threats:		2014-15 U.S./2014 Europe, Canada/2018 Japan
2024 Sales	Morningstar	$1,079 million
	Consensus	$1,077 million
Market Model:		—

Nexium will continue to erode due to increasing generic competition, but a strong brand name should give the drug a tail in emerging markets. Also, Astra's pricing cuts are helping to keep some volume (OTC sales help the royalty sales line as well in the U.S.). Sales in China are still driving growth despite pressures on other older brand name drugs.

Product:		Symbicort
Composition:		small molecule (ICS/LABA)
Economics:		—
Therapeutic Area:		COPD
Patents/Generic Threats:		2014-26 for most patents
2024 Sales	Morningstar	$1,602 million
	Consensus	$1,718 million
Market Model:		nonbiologic respiratory (p.170)

While the exact timing of generic Symbicort is difficult to project due to the complexity of its lung delivery and typically weaker patents having stronger position in respiratory disease, the new branded drugs and pricing pressures from payers will weigh on the drug. Also, the approval of a generic Advair in 2019 will increase pricing pressures as payers push for use of the similar generics. However, sales in China are still driving growth despite pressures on other older brand name drugs.

Product:		Pulmicort
Composition:		small molecule (ICS)
Economics:		—
Therapeutic Area:		COPD
Patents/Generic Threats:		2018-19 U.S./2018 International
2024 Sales	Morningstar	$1,110 million
	Consensus	$1,591 million
Market Model:		nonbiologic respiratory (p.170)

The majority of patents have expired, but sales remain strong in emerging markets. Sales in China remain robust despite increasing pressure from the government to push down prices.

Product:		Brilinta
Composition:		small molecule (P2Y12)
Economics:		—
Therapeutic Area:		cardiovascular
Patents/Generic Threats:		2021-24 U.S./2019 Canada, Japan/2024 Europe
2024 Sales	Morningstar	$1,493 million
	Consensus	$1,949 million
Market Model:		—

Brilinta is a maturing asset driven by multiple cardiovascular indications. Plato (Acute Coronary Syndrome/ACS versus Plavix, $2 billion potential with positive data), Pegasus (long-term use in ACS versus placebo, $2 billion potential with positive data), Themis (diabetes versus Placebo, $5 billion) and Thales (stroke, positive data in Jan. 2020, $2 billion) should drive further growth ahead of the eventual patent loss.

Inline Drugs

Product:		Farxiga
Composition:		small molecule (SGLT2)
Economics:		close to 20% royalty to BMY
Therapeutic Area:		diabetes
Patents/Generic Threats:		2020-26 U.S./2020-28 international
2024 Sales	Morningstar	$2,630 million
	Consensus	$3,032 million
Market Model:		non-insulin diabetes (p.175)

Farxiga's diabetes outcomes data (Declare) was mixed (hit one primary endpoint of heart failure or death but missed another primary endpoint of MACE), but the FDA approved this indication in October 2019 as did the EMEA in August 2019. Also, August 2019 data in heart failure (reduced ejection) in patients with or without diabetes was strong, with 26% improvement in cardiovascular death/hospitalization (better than Novartis' Entresto of 20%). The FDA approved the heart failure indication in May 2020. Patients in developed markets and China on treatment for type 2 diabetes (100 million) and reduced ejection heart failure (12 million)11 should set up a strong potential for the drug at a price of close to $5,000 a year in the U.S.

Astra is trying several combos, including SGLT2 plus GLP1, and trying Farxiga in chronic kidney disease (phase 3 data was positive in March 2020 for diabetics and non-diabetics) and chronic heart failure (phase 3 2021+ for preserved ejection).

Product:		Tagrisso
Composition:		small molecule (EGFR)
Economics:		—
Therapeutic Area:		cancer
Patents/Generic Threats:		2032 U.S./international
2024 Sales	Morningstar	$7,702 million
	Consensus	$7,119 million
Market Model:		—

Tagrisso has expanded from the initial focus of targeting non-small cell lung cancer (NSCLC) with T790M+ status (T790 mutation status affects close to 60% of EGFR+ lung cancers, which is about 20-30% of total lung cancer) to the broader first-line EGFR+ setting based on study Flaura (head to head versus Tarceva showing a 54% benefit on progression free survival) that was added to global developed market labels in mid-2018, followed by China in September 2019. The first-line opportunity increases the opportunity (40,000 second line T790M patients to 250,000 EGFR patients in developed world and China12) and should support sales over Astra's historical expectation of non-risk-adjusted peak sales of $3 billion. The $150,000-a-year price for Tagrisso versus Tarceva (priced at $36,000 and going generic in 2018-20E) will help drive these peak sales. Sales growth should slow in the U.S. where the first-line market is 70% penetrated by Tagrisso, but other regions are still growing fast. Also, the Adaura study in adjuvant EGFR cancer read out positively in April 2020 (two years ahead of schedule and detailed data at ASCO in June 2020) opening up more potential patients (40% of lung cancer patients diagnosed in the adjuvant setting.) In Adaura, the primary endpoint of disease-free survival showed the drug to have a benefit of 83%.

11 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

12 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

Product:		Onglyza
Composition:		small molecule (DPPIV)
Economics:		close to 20% royalty to BMY
Therapeutic Area:		diabetes
Patents/Generic Threats:		2023 U.S./2024 Europe
2024 Sales	Morningstar	$333 million
	Consensus	$307 million
Market Model:		non-insulin diabetes (p.175)

Onglyza's acute heart failure risk (Tecos data) is likely to diminish the drug's place in the DPPIV class, and Astra has shifted marketing focus to Farxiga.

Product:		Lynparza
Composition:		small molecule (PARP)
Economics:		50% of profits to Merck
Therapeutic Area:		cancer
Patents/Generic Threats:		2028 U.S./2021-27 international
2024 Sales	Morningstar	$3,254 million
	Consensus	$3,561 million
Market Model:		—

With approvals in first- and second-line ovarian cancer, breast cancer, and strong first-line ovarian cancer data in Solo-1 (PFS HR of 0.30), the drug is already well positioned in these BRCA mutated patients (15% of all ovarian, 2%-10% of breast)13.

The FDA approval in early 2020 for pancreatic cancer followed by EU approval in July 2020 (4-7% have BRCA mutations)14 with strong data (PFS HR of 0.53) adds more potential. The PAOLA-1 study with Avastin (FDA approved in May 2020) adds more first-line ovarian patients (BRCA and HRD+, 65% of the market, but not HRD- patients where competitor Zejula from GSK will likely have an advantage) with strong PFS HR data (0.31-0.33 in BRCA or HRD+ versus data seen from Glaxo's competitive drug Zejula 0.40-0.43). Also, Profound (2L prostate cancer data reported Aug. 2019 and FDA approved in May 2020) had solid data (PFS HR of 0.34 and a positive OS benefit in BRCA and PFS HR of 0.49 in homologous recombination repair (HRR) mutations with a survival benefit) and should add more potential patients in all homologous recombination repair HRR patients (1-2% of prostate patients have a BRCA mutation, which is a subset of HRR that represents close to 20-30% of prostate cancers)1516. Note HRD is short for HRR deficiency.

With developed markets and China having large numbers of treated patients in ovarian (84,000 first line of which 18,000 have BRCA mutation), breast (45,000 BRCA), pancreatic (10,000), and prostate cancers (1,000 BRCA 2nd line and 10,000 HRR), the drug holds strong potential and is priced at close to $150,000 a year in the U.S.17

Additional phase III studies with Zytiga in "all comers" prostate cancer (data in 2021) and as monotherapy in adjuvant HER2- BRCA breast cancer (data in 2022) could add to the label. Data in lung cancer should ready in 2024. Other approved PARPs Rubraca and Zejula appear to have similar efficacy and safety but look behind Lynparza on timing of approvals.

13 BRCA mutation in high grade epithelial ovarian cancers, Manchana, Tarinee et al., August 2019, Dana Farber Cancer Institute, Rana, Huma, June 2019.

14 National Cancer Institute, Trial Highlights Complexities of Targeted Therapy for Pancreatic Cancer

15 Androl, Asian The role of BRCA1 and BRCA2 in prostate cancer, 2012.

16 Li et al. Homologous recombination in DNA repair and DNA damage tolerance. Cell Research, 2008.

17 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

Product:		Bevespi
Composition:		small molecule (LABA/ LAMA)
Economics:		—
Therapeutic Area:		COPD
Patents/Generics Threats:		2023
2024 Sales	Morningstar	$444 million
	Consensus	$372 million
Market Model:		nonbiologic respiratory (p.170)

The growing competitive landscape in COPD will probably limit the sales potential for Bevespi. However, the company's strong entrenchment with Symbicort and the drug's efficacy advantage over Spiriva should help the drug on a pathway to peak sales approaching $1 billion. Also, the liquid formulation should help with severe patients or weak patients. However, Astra's expectations of peak sales of $4 billion seem unrealistic. The FDA approved the drug in April 2016 and Europe approved the drug in December 2018. Also, the drug failed to show efficacy as good as Anoro, which will hurt the drug's potential.

Product:		Calquence/acalabrutinib
Composition:		small molecule (BTK)
Economics:		from majority stake in Acerta Pharma
Therapeutic Area:		CLL, MCL
Patents/Generics Threats:		2032
2024 Sales	Morningstar	$2,099 million
	Consensus	$2,154 million
Market Model:		CLL (p.187)

Astra's BTK inhibitor Calquence (acalabrutinib) received accelerated approval in treatment in adults with mantle cell lymphoma (MCL) in late 2017, but the real sales potential for the drug is with the Nov. 2019 FDA approval in chronic lymphocytic leukemia (CLL), patients. Calquence will need to take share from AbbVie's/JNJ's Imbruvica (approved in 2014 for CLL). Calquence posted progression free survival (PFS) improvements of 69% (refractory mono versus Rituxan plus Idelalisib or Rituxan plus Bendamustine) and 90% (first line combined with Gazyva versus Gazyva plus chlorambucil). Imbruvica posted PFS improvements of 78% (refractory versus Arzerra) and 77% (first line combined with Gazyva versus Gazyva plus chlorambucil). Safety looks slightly better with Calquence with serious adverse rates of 39% versus 58% for Imbruvica in the first line setting with atrial fibrillation a key outlier (3% versus 12% for Imbruvica), but headache and bleeding rates were better for Imbruvica. A head to head study versus Imbruvica should report out in March 2021 in the refractory CLL patient group.

Developed markets and China have large numbers of treated patients in first line CLL (33,000) and second line CLL (27,000). Combined with an annual price of close to $180,000, the drug holds solid potential.18

Product:		Imfinzi/durvalumab
Composition:		biologic (PD-L1)
Economics:		blood cancer development externalized to Celgene
Therapeutic Area:		cancer
Patents/Generics Threats:		2030
2024 Sales	Morningstar	$5,534 million
	Consensus	$4,050 million
Market Model:		immuno-oncology (p.181)

Despite launching late to the immuno-oncology market and failing in the Mystic and Neptune lung studies, Imfinzi still holds solid potential. Imfinzi remains well positioned in the smaller stage 3 lung cancer subsegment due to the positive Pacific data, which still represents close to a $2 billion opportunity. In Europe, the drug only received a PDL1+ stage 3 lung cancer label. Pacific 2 in stage 3 lung cancer (radiation use concurrently rather than sequentially in Pacific) should read out in 2020. The small cell lung cancer data (OS HR of 0.75 in extensive disease) supported U.S. approval in the patient group in March 2020 and a Phase III study in SCLC limited disease (Adriatic) should report in 2021. However, the combination with CTLA4 drug tremelimuab didn't work in SCLC.

Developed markets and China have large numbers of treated patients in stage III non-small cell lung cancer (240,000) and small cell lung cancer (limited 55,000 and extensive 160,000). Combined with an annual price of close to $150,000, the drug holds potential.19

Key upcoming data points include OS data from Poseidon (+chemo in first-line lung, 2021, and PFS was positive). Phase III studies in neo-adjuvant lung and head and neck cancer should report in 2020. Renal cancer and adjuvant NSCLC lung studies should report in 2021.

18 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

19 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

Product:		Fasenra/Benralizumab
Composition:		biologic (IL-5)
Economics:		—
Therapeutic Area:		asthma/COPD
Patents/Generics Threats:		2020-34
2024 Sales	Morningstar	$1,827 million
	Consensus	$2,166 million
Market Model:		biologic respiratory (p.171)

Benralizumab (priced at close to $30,000 a year following first year) competes against GSK's Nucala and Teva's Cinqair and targets the IL-5 receptor instead of IL-5 itself. Dosing (first three doses every three weeks, followed by dosing every eight weeks) could be an advantage. The drug failed in two different phase 3 studies for COPD patients.

Product:		Lokelma/ZS-9
Composition:		small molecule (potassium binder)
Economics:		from ZS Pharma acquisition
Therapeutic Area:		hyperkalemia (high potassium)
Patents/Generics Threats:		Early 2030s
2024 Sales	Morningstar	$1,002 million
	Consensus	$523 million
Market Model:		—

With over 3 million people in the developed markets with stage 4 or 5 CKD (leading cause of hyperkalemia), we expect Lokelma/ZS-9 to develop into a $1 billion product in line with management expectations. With two successful phase 3 studies controlling potassium levels, the drug reached the market in mid-2018 (priced at close to $9,000 a year) after fixing manufacturing issues in Coppell, Texas, that caused a delay in approval. Fixing the issues was complicated by the need for high heat in manufacturing. Also, with no drug-drug interactions, Lokelma is well positioned against recently approved Veltassa, which carries a black box warning on drug-drug interactions and has faster time to onset (1 hour versus 7 for Veltassa).

Product:		Enhertu/DS-8201
Composition:		Biologic (ADC HER2+)
Economics:		$5.5B to Daichi 50/50 profit split
Therapeutic Area:		cancer
Patents/Generics Threats:		
2024 Sales	Morningstar	$900 million
	Consensus	$583 million
Market Model:		—

Enhertu is a drug similar to Roche's breast cancer drug Kadcyla, but appears to offer a stronger effect and broader potential beyond breast cancer. In early studies, the drug showed a 60% response rate in breast cancer patients that had 7 previous lines of therapy (including Kadcyla). Kadcyla has shown 21-44% response rates in much healthier patients. The stronger effect can also open up HER2 low patients with response rates of 33-55% versus 20% for Ibrance (in healthier patients). Beyond breast cancer, other HER2+ cancers could response as well with excellent data in gastric (phase 2 OS HR of 0.59 in HER2+ refractory patients). The drug was approved in the refractory breast cancer setting in late 2019 and priced at $150,000 per year. Phase II data in gastric is strong enough for a likely filing in 2020. Phase 3 2021 readouts in Destiny-2 (third line breast), Destiny-3 (second line breast), and Destiny-4 (HER2 low) should support further filings. On the side effect side, lung scarring (interstitial lung disease ILD) is partly concerning but looks manageable.

Product:		Koselugo/Selumetinib
Composition:		small molecule (MEK inhibitor)
Economics:		50% of profits to Merck
Therapeutic Area:		Cancer
Launch Year/Probability:		2020/100%
2024 Sales	Morningstar	$120 million
	Consensus	$215 million
Market Model:		—

While Astra is a bit late to the MEK space, we believe combination usage with other Astra drugs holds potential, but reaching more than $1 billion in sales (historical management guidance) may be tricky following the drug's setbacks, including a phase 3 failure (Sumit) in its original indication, uveal melanoma, and a failure in a phase 3 trial (Select-1) in combination with chemotherapy in patients with second-line KRAS mutation-positive advanced or metastatic NSCLC. However, good phase 2 data (66% overall response rate) at ASCO 2018 in NF1 (an incurable generic condition that impacts 1 in 3,000-4,000 people) gives the drug more potential. The drug was filed with the FDA in Nov. 2019 and approved in April 2020 with a monthly price of $12,000, suggesting a relatively modest peak sales potential (potentially $500 million a year globally) in the first indication, but the firm did gain a rare pediatric disease priority review voucher.

Moat Trend and Product Pipeline

Product:		Roxadustat
Composition:		small molecule (HIF-PH)
Economics:		FibroGen-tiered royalty in low 20s in U.S./China, no rights in Europe/Japan
Therapeutic Area:		anemia/CKD
Launch Year/Probability:		2020/90%
2024 Sales	Morningstar	$586 million
	Consensus	$863 million
Market Model:		—

While early-stage data looks good in smaller patient sets, EPO is relatively easily taken with good efficacy, so any side effect issues could derail this drug. In phase 3 studies Olympus (nondialysis versus placebo) and Rockies (dialysis versus Epogen), the drug met its primary efficacy endpoints in improvement in hemoglobin levels averaged over 28-52 weeks, but the data is less clear in hard endpoints like MACE (except in recently started dialysis patients that showed good data).

The drug is unique in that it allows the integration of red blood cell production and the incorporation of iron simultaneously rather than managing this separately with ESAs and iron dosing. Roxadustat entered pivotal development ahead of competitors in the renal anemia market such as Daprodustat and Vadadustat. China approved the drug in December 2018. The drug was accepted by the FDA in Feb. 2020. In the U.S., there are 515,000 dialysis and 1.5 million non-dialysis-treated patients, suggesting a large patient group. In China, there are 1.5 million treated anemia patients.

Product:		Anifrolumab
Composition:		biologic (Type 1 IFN)
Economics:		—
Therapeutic Area:		lupus
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	$280 million
	Consensus	$235 million
Market Model:		—

Phase 2 data showed SRI benefit of 26%, which is good, but that is not much better than Benlysta's around 20%. One of two pivotal phase 3 studies Tulip 1 failed to show a benefit, but the second study (Tulip 2) showed favorable data. Also, had Tulip 1 used the same endpoint as Tulip 2, the data would have been favorable. Major side effects included herpes and one death due to pneumonia. Despite the mixed data, we expect the drug will reach the market given the lack of treatment options. Astra plans to file the drug late in 2020. In the top 8 developed countries, there are 320,000 moderate to severe treated patients, with 30,000 using a biologic.

Product:		Tremelimumab
Composition:		biologic (CTLA-4)
Economics:		—
Therapeutic Area:		cancer
Launch Year/Probability:		2022/70%
2024 Sales	Morningstar	$450 million
	Consensus	$235 million
Market Model:		—

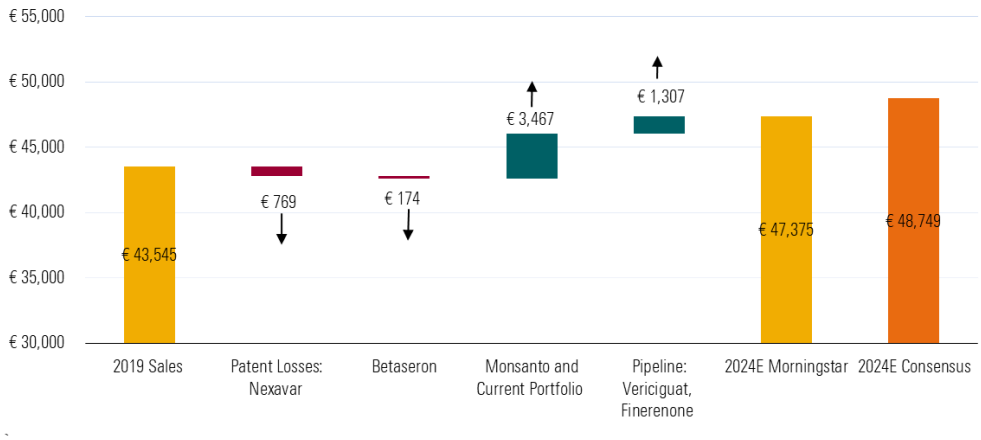
The setbacks with the drug in the Mystic and Neptune studies and failure in monotherapy are concerning, but early-phase combination data still supports the likely approval of the drug in combination with Imfinzi. Also, positive data from Poseidon with PFS could lead to a positive OS benefit (data expected in 2021).

Product:		PT010/Triple LAMA/LABA/ICS	In 2013, Astra acquired Pearl Therapeutics for $560 million (and milestones up to $450 million) for a LAMA/LABA and a LAMA/LABA/ICS. With the respiratory market growing increasingly competitive, we believe it will be difficult for the drug to show enough differentiation to gain significant market share. Strong phase 3 data in COPD was presented in early 2018. The asthma indication is still in earlier stage development. While the drug was approved in Japan in mid-2019, Astra received a complete response letter from the FDA in Oct. 2019, asking for more clinical data. Astra expects a decision by the FDA based on new data provided by late 2020.
Composition:		Small Molecule	
Economics:		—	
Therapeutic Area:		respiratory (COPD first)	
Launch Year/Probability:		2019-20/80%	
2024 Sales	Morningstar	$330 million	
	Consensus	No estimate	
Market Model:		nonbiologic respiratory (p.170)	
Product:		tezepelumab	Tezepelumab is currently in phase 3 studies in severe uncontrolled asthma and steroid-dependent asthma (data expected late 2020), and if approved, we expect it could see a leading share in the severe asthma setting, where 2 million patients in major markets are uncontrolled and only 15% receive a biologic. TSLP is an upstream driver of airway inflammation. In the phase 2b Pathway study, tezepelumab showed excellent efficacy and safety in patients uncontrolled on inhaled corticosteroids and LABA, with significant 61%-71% reductions in asthma exacerbation rates versus placebo at various doses at 52 weeks. The drug appears to impact IL-4, IL-5, and IL-13 pathways. The reductions were significant regardless of subpopulation, and the study included both high and low eosinophil count patients, which should differentiate the drug from IL-5 antibodies like Astra's Fasenra and Glaxo's Nucala, where only 50% of patients—those with high eosinophil counts—are eligible. Dupixent looks like the key competitor, as it recently received a wider approval in asthma patient dependent on steroid treatment. Patents run through 2029 in the U.S. and 2028 in Europe.
Composition:		biologic (TSLP antibody)	
Economics:		split ~ 60/40, Amgen/Astra	
Therapeutic Area:		severe asthma	
Launch Year/Probability:		2021/60%	
2024 Sales	Morningstar	$450 million	
	Consensus	$370 million	
Market Model:		biologic respiratory (p.171)	
Product:		Capivasertib	Capivasertib is in phase 3 development for triple negative breast cancer with data likely in mid-2022. Data at ASCO 2019 showed an OS HR of 0.57 in an early stage study with patients with metastatic ER positive breast cancer.
Composition:		small molecule (AKT inhibitor)	
Economics:			
Therapeutic Area:		Cancer	
Launch Year/Probability:		2022	
2024 Sales	Morningstar	Not meaningful (in other sales)	
	Consensus	--	
Market Model:			
Product:		Brazikumab	Astra gains rights to brazikumab from Allergan who needed to return the rights of the drug back to Astra. Allergan needs to pay for the phase 3 clinical trials. Phase 3 data should be ready in late 2022 in Crohn's disease. Phase 2 data in ulcerative colitis should be ready in 2020.
Composition:		biologic IL23	
Economics:		High single-digit to low double-digit royalty to Amgen	
Therapeutic Area:		immunology	
Launch Year/Probability:		2023	
2024 Sales	Morningstar	$150 million	
	Consensus	--	
Market Model:		psoriasis (p. 166), crohn's/UC (p. 168)	
Product:		Nirsevimab/MEDI8897	Nirsevimab is a longer-acting antibody than established respiratory syncytial virus (RSV) prophylaxis antibody Synagis, with a broader potential group of infants (including full-term infants) eligible for treatment. Phase 2b data showed nirservimab lowered RSV rates (70%) and RSV-related hospitalizations (78%). While the data looks good, phase 3 data is needed to confirm the efficacy and safety. Phase 3 data in high risk infants is expect in 2021 followed by healthy infants by 2023. Pfizer is also looking to bring an RSV vaccine to the market, likely around the same time.
Composition:		antibody	
Economics:		Profit share with Sanofi, SOBI	
Therapeutic Area:		RSV prevention	
Launch Year/Probability:		2024/25%	
2024 Sales	Morningstar	Not meaningful (in other sales)	
	Consensus	--	
Market Model:			

Bayer BAYRY

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$26.00	0.73	High	Wide	Stable

Revenue Breakdown EUR Millions



Source: Morningstar, company reports, and DrugAnalyst/S&P Cap IQ for consensus.

Strong Growth Potential for Xarelto and Only Minor Patent Losses Drive Sales

Expiring Patents

Bayer faces very little generic competition over the next five years, but concern is mounting for the Xarelto patent loss starting in 2024 in some countries.

Inline Products

We expect steady growth from Xarelto (based on label expansion) and several recently launched cancer drugs (Nebeqa and Vitrakvi). Also, Eylea should provide some stability over the next five years as emerging competition doesn't look too differentiated, but we expect some mild market share loss. Bayer diverse operations in crop science should provide steady gains.

Pipeline

While the late-stage pipeline is fairly weak, kidney drug finerenone could be a major drug if the phase 3 data is positive. Otherwise, Bayer needs to move its early stage drugs along faster.

Moat and Product Portfolio

Inline Products

Product:		Xarelto
Composition:		small molecule (factor Xa)
Economics:		royalty from J&J for U.S. sales, up to 30% of sales
Therapeutic Area:		deep vein thrombosis
Patents/Generic Threats:		2027 U.S./2024 international
2024 Sales	Morningstar	EUR 3,944 million
	Consensus	EUR 3,234 million
Market Model:		atrial fibrillation (p.172)

Xarelto's once-daily dosing/first mover advantage in AF, DVT/PE, and ACS (EU)—a $20 billion-plus market—should net 30% share (up from 25% currently) versus PFE/BMY's Eliquis netting 50%+ (up from 45% currently, twice daily dosing, but with mortality benefit) and warfarin (20% market share currently). The positive data in PCI (Pioneer versus warfarin) and coronary artery disease (CAD) and peripheral artery disease (PAD) (Compass versus aspirin) should add $3 billion and $10 billion in market potential, respectively. The Compass data showed a 24% MACE reduction, good compared with statins (20%-30%), GLP-1 (low to mid-20s), SGLT-2s (midteens), and PCSK-9s (15%). However, educating physicians to use an anticoagulant in CAD/PAD has proved challenging and uptake has been slow. Important label expansion opportunities should produce data over the next few years, including PAD (Voyager, $2 billion opportunity, 2020) and several smaller patient population studies.

Product:		Kogenate/Kovaltry/Jivi
Composition:		biologic (coagulation factor VIII)
Economics:		low-single-digit royalty payments in aggregate
Therapeutic Area:		hemophilia A
Patents/Generic Threats:		2017-24, (2025 for Jivi)
2024 Sales	Morningstar	EUR 740 million
	Consensus	EUR 821 million
Market Model:		hemophilia (p.173)

Bayer's hemophilia A portfolio includes several drugs. Kogenate and Kovaltry are older Factor VIII drugs, but the lack of desire for switching should mean a long tail of demand for the drugs. However, increasing unique competition will likely mean a shrinking tail of revenue. Jivi (BAY-94-9027) has a longer duration of action with relatively similar efficacy to Kogenate, which should help Bayer mitigate market share losses in the hemophilia market from Roche and Alnylam's novel treatments. Jivi is dosed 2 times weekly or every seven days.

Product:		Eylea
Composition:		biologic (VEGF)
Economics:		50/50 profit split with Regeneron on sales OUS, no U.S. rights
Therapeutic Area:		ophthalmology
Patents/Generic Threats:		2020 (Canada, China), 2025 international
2024 Sales	Morningstar	EUR 2,053 million
	Consensus	EUR 2,512 million
Market Model:		—

Eylea market shares in Europe and Japan (no off-label Avastin) are over 40% and 70%, respectively (as high as 70% in the U.K.), but more EU countries are allowing off-label Avastin. However, competition is coming from Novartis' Beovu/RTH258 (approved in late 2019). In the key phase 3 studies Hawk and Harrier, RTH258 was noninferior to Eylea in age-related macular degeneration. Additionally, 52%-57% of RTH258 patients were able to follow a 12-week dosing regimen versus eight-week dosing for Eylea (after loading doses for both). Bayer and Regeneron gained a label expansion in Europe in August 2018 for Eylea for 12-week dosing based on this dosing working for 60% of patients in the ALTAIR study.

Product:		Aliqopa/Copanlisib
Composition:		small molecule (PI3K)
Economics:		—
Therapeutic Area:		cancer
Patents/Generic Threats:		2032
2024 Sales	Morningstar	EUR 367 million
	Consensus	EUR 404 million
Market Model:		NHL (p.185)

Bayer's PI3K inhibitor, Aliqopa (Copanlisib) has been approved in relapsed follicular lymphoma patients (which accounts for about 35% of non-Hodgkin's lymphoma) who have received at least two prior treatments. Additional studies will have further implications for the drug; Chronos-2 (small informational study) tests Aliqopa versus placebo in patients with Rituxan refractory indolent non-Hodgkin's lymphoma (data 2020), and Chronos-3 will look at Aliqopa in combination with Rituxan in iNHL patients who have relapsed after one prior therapy (data in August 2020). Bayer estimates peak sales of EUR 500 million, which seems reasonable.

Product:		Vitrakvi/larotrectinib
Composition:		small molecule (TRK)
Economics:		50/50 profit split with Loxo
Therapeutic Area:		cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	EUR 432 million
	Consensus	EUR 461 million
Market Model:		—

Vitrakvi is an oral small-molecule drug with high selectivity for tropomyosin receptor kinases, or TRKs. The drug was approved in late 2018 in the U.S. at a price of $400,000 per year. Approval followed in Europe (Sept. 2019). The indication is for cancers that have TRK gene fusion (0.5%-1% of all solid tumors). Bayer expects peak sales from the drug of over EUR 750 million, which looks likely. Competition in the TRK fusion market looks manageable; Roche's entrectinib had a 57% response rate in its TRK-fusion trial, which did not stack up well against Bayer/Loxo's larotrectinib's 81% response rate in a similar population, although Roche's trial included many patients with CNS metastases and lacked pediatric patients, potentially weighing on its performance.

Product:		Nubeqa/darolutamide/ODM-201
Composition:		small molecule (androgen receptor)
Economics:		double-digit royalties to Orion
Therapeutic Area:		prostate cancer
Patents/Generic Threats:		2030
2024 Sales	Morningstar	EUR 553 million
	Consensus	EUR 679 million
Market Model:		—

Darolutamide seems to lack much differentiation in an increasingly crowded space of androgen receptor drugs (Zytiga and Xtandi). Not crossing the blood-brain barrier could reduce risks of side effects like seizures, but these side effects don't seem overly problematic for Zytiga and Xtandi. While management expects over EUR 1 billion at peak, we are skeptical of this estimate. The data from phase 3 study Aramis (high-risk nonmetastatic prostate cancer) showed a metastasis free survival HR of 0.41, slightly worse than .29-.30 for competitive drugs from Pfizer and J&J. However, the OS benefit improved by 31%, which is better than J&J's Erleada (22% benefit) and Pfizer's Xtandi (27% benefit). Also, the phase 3 study Arasens (metastatic prostate cancer) should read out in 2022. The drug was approved in the U.S. in July 2019, followed by Japan in Jan. 2020 and Europe in March 2020.

Moat Trend and Product Pipeline

Product:		finerenone
Composition:		small molecule (MRA)
Economics:		—
Therapeutic Area:		diabetic nephropathy
Launch/Probability:		2021/50%
2024 Sales	Morningstar	EUR 328 million
	Consensus	EUR 307 million
Market Model:		—

The drug holds strong potential but also carries a high risk due to regulatory agencies focused on any side effects in such large indications. In a phase 2 study with 1,500 patients with diabetic nephropathy, the drug achieved the primary endpoint in reducing the urinary albumin to creatinine ratio in the four highest doses; hyperkalemia was higher with these groups, too (2%-3%), though still below spironolactone. Two phase 3 studies (Fidelio and Figaro in CKD) should complete in mid-2020 and mid-2021, respectively, but the studies are event driven. The Fidelio study posted positive topline data in July 2020 with details expected in late 2020. New phase 3 study Finearts-HF was started in 2020 to evaluate the drug in symptomatic heart failure with a left ventricular ejection fraction of $\geqslant$40%.

Product:		vericiguat
Composition:		small molecule (sGC)
Economics:		50/50 profit split with Merck
Therapeutic Area:		heart failure
Launch/Probability:		2021/30%
2024 Sales	Morningstar	EUR 200 million
	Consensus	EUR 206 million
Market Model:		—

Vericiguat is thought to act on the nitric oxide soluble guanylate cyclase (sGC) to help treat heart failure, but the failed phase 2 study Socrates in heart failure patients doesn't give us much confidence in the drug. However, the phase 3 study (Victoria) in reduced ejection fraction heart failure reported positive date with a 10% reduction in hospitalization or cardiovascular death, which was statistically significant but is only marginally clinically relevant. In the patient population with low levels of NT-proBNP (biomarker seen in 75% of the study group), the drug effectiveness improved to 18-27%, which is much better. A phase 2 study in preserved heart failure should complete in 2020. The drug was submitted to European and Japanese regulators in June 2020.

Product:		molidustat
Composition:		small molecule (hypoxia inducible factor prolyl hydroxylase)
Economics:		—
Therapeutic Area:		kidney disease
Launch/Probability:		2022/30%
2024 Sales	Morningstar	$188 million
	Consensus	$73 million

With a similar mechanism action as an Astra pipeline drug and a relatively good treatment with EPO already approved, the hurdle rate for approval and market acceptance is higher than average. Nevertheless, the early data on phase 2 program Dialogue looks solid. The current ongoing phase 3 studies are small in size and don't seem large enough to support a global filing but could work for a Japanese filing. Bayer doesn't plan to do a global launch for the drug but might partner the drug for regions outside of Japan.

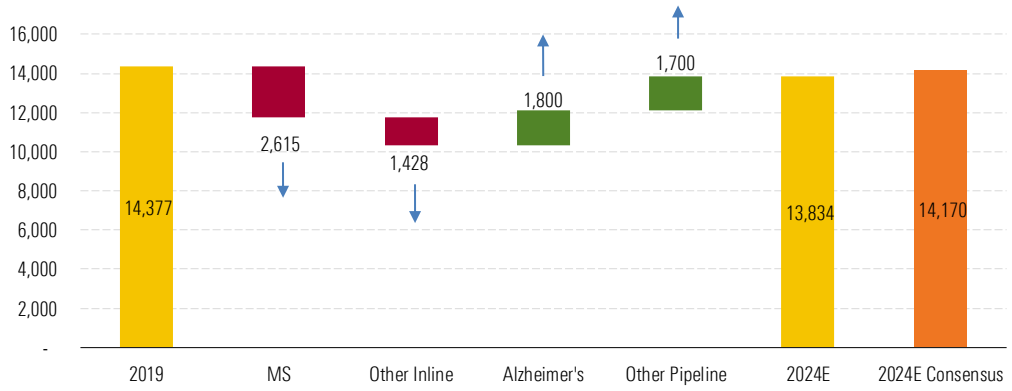
Product:		vilaprisan
Composition:		small molecule (progesterone modulator)
Economics:		—
Therapeutic Area:		uterine fibroids
Patents/Generic Threats:		2022/20%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	$69 million
Market Model:		—

The two phase 3 trials Asteroid 5 (safety of Vilaprisan in subjects with uterine fibroids compared with Ulipristal) and Asteroid 6 (efficacy of Vilaprisan in subjects with uterine fibroids) were expected to complete in 2021. However, data in late 2018 suggested that the drug may have unacceptable toxicology data, which has led to a clinical trial hold by the company, which is still in effect as of early 2020. While AbbVie is working on a drug for this target group as well, the mechanisms of action are very different.

Biogen BIIB

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$389.00	0.69	High	Wide	Stable

Revenue Breakdown USDMillions



Source: Morningstar, company reports, and DrugAnalyst/Visible Alpha for consensus.

Ocrevus Royalties, Strong Neurology/Ophthalmology Pipeline Counter Spinraza, Older MS Drugs

Expiring Patents

Biogen's oldest multiple sclerosis drugs Avonex and Tysabri have matured and are declining as they face competitors with improved efficacy or safety profiles. Biogen's Tecfidera-related patent litigation is continuing, and we still model sales in 2024 below consensus following a recent Mylan litigation loss. While Rituxan is seeing biosimilar pressure, we think the Gazyva profit share (patents through 2030) and Ocrevus royalty stream offset pressure on payments from Roche.

Inline Products

We expect Biogen's $9 billion in MS revenue to see low-single-digit annual declines beginning in 2021 as new competition and pricing pressure weigh on sales, but with pharmacy benefit managers somewhat constrained in restricting usage of MS therapies, given the heterogeneity of the disease. We assume that sales of spinal muscular atrophy drug Spinraza peaked at $2.1 billion in 2019, and our 2024 projections are below consensus as we expect Novartis and Roche to steal share and weigh on price.

Pipeline

Biogen's pipeline potential is clearly led by aducanumab, but several other programs are poised to produce data through the end of 2021. In 2020, data for novel MS drug opicinumab, Parkinson's antibody cinpanemab, stroke drug TMS-007, and ophthalmology gene therapy timrepigene emparvovec could drive more bullish sentiment, although all are still high-risk/high-reward programs. We continue to model probability weighted sales (at 40% probability of approval) of $3 billion for aducanumab by 2029, assuming potential approval in 2021.

Moat and Product Portfolio

Expiring Patents

Product:		Tecfidera
Composition:		small molecule
Economics:		milestones to Fumapharm
Therapeutic Area:		MS
Patents/Generic Threats:		2021 U.S. ('514 patent settlements prior to Feb 2028 expiration, assume Mylan launch 2021) 2024 EU (exclusivity--2029 patent revoked)
2024 Sales:	Morningstar	$1.0 billion
	Consensus	$3.3 billion
Market Model:		MS (p.177)

With efficacy on par with other leading oral therapy Gilenya and a strong safety profile despite rare reported PML cases, we think Tecfidera remains well positioned, but increased competition in the S1P class of orals (Bristol's Zeposia approved March 2020, J&J's ponesimod was filed in March 2020) as well as in-house competition from Biogen/Alkermes' Vumerity (better GI profile) will weigh on Tecfidera demand, and we model high-single-digit annual declines. However, the pushback of expected generic Gilenya entry (from 2019 to 2027) should secure Biogen's pricing power until patent settlements dictate, despite the April 2020 approval of Banner's bioequivalent drug Bafiertam (the drug isn't substitutable). Given the June West Virginia decision finding in favor of Mylan ('514 patent invalid), we now expect generic headwinds in 2021 in the U.S. (Mylan expects FDA approval in Nov 2020). Before the West Virginia decision, U.S. protection looked likely to stand until close to 2028, given positive U.S. IPR and Forward Pharma litigation rulings in 2017, and another positive IPR ruling (filed by Mylan) in Feb 2020. However, we knew that district court rulings in Delaware (decision 2020E) and West Virginia could move the timeline for generic launches earlier, and some settlements already resulted in earlier agreed launch dates. Biogen's method-of-use patent has been revoked in Europe (appeal hearing March 2020), and so has Forward Pharma's European patent (appeal hearing June 2020); the Forward Pharma patent could result in protection through 2028 and a 10% ex-U.S. royalty obligation (for now, we assume European protection ends with regulatory exclusivity in 2024).

Inline Products

Product:		Avonex/Plegridy
Composition:		biologic (recombinant protein)
Economics:		—
Therapeutic Area:		MS
Patents/Generic Threats:		2026 U.S. (method of use)/EU: Avonex expired, Plegridy exclusivity 2024
2024 Sales:	Morningstar	$1.4 billion
	Consensus	$1 billion
Market Model:		MS (p.177)

Biogen's core MS injectables see eroding demand due to orals (Tecfidera), high-efficacy injectables (Ocrevus), and generic Copaxone (Mylan's 3 times/week version launched 2017), but Plegridy's every-two-weeks dosing should allow it to dominate a shrinking interferon market. Avonex and Plegridy were both excluded from CVS formularies in 2016-17 (24% of U.S. covered lives) but added back in 2018, and we think payers are hesitant to force switching in this heterogeneous patient population, which allows Biogen some U.S. pricing leverage. Biogen has also filed for approval of an intramuscular version of Plegridy in 2020, which was found to reduce injection site reactions (a key driver of discontinuations) by more than 50% versus the approved subcutaneous administration.

Product:		Rituxan/Gazyva (U.S.)
Composition:		biologic (antibody)
Economics:		35%-40% share of U.S. profits (from Roche)
Therapeutic Area:		oncology (NHL/CLL), arthritis
Patents/Generic Threats:		U.S.: 2018 Rituxan, 2030 Gazyva
2024 Sales:	Morningstar	$800 million
	Consensus	$850 million
Market Model:		CLL (p.187), NHL (p.185)

While Rituxan sales are declining as biosimilars entered the U.S. market in late 2019, Biogen also receives a U.S. profit share on next-generation antibody Gazyva, which has shown superiority to Rituxan for indications covering 70% of the drug's current usage in oncology and was approved for use in the largest setting (first-line follicular lymphoma). Gazyva could see increased use in CLL in combination with BTK inhibitors (Astra's Calquence combo approval expected in 2020, AbbVie/J&J's Imbruvica Jan 2019 approval) or AbbVie/Roche's Venclexta (combo approved May 2019). Gazyva also has potential in lupus nephritis based on recent phase 2 data, and Roche is moving forward with phase 3 studies (see Roche section for more details).

Product:		Spinraza/nusinersen (ISIS-SMNRx)
Composition:		small molecule (antisense oligonucleotide)
Economics:		in-licensed (midteens royalties to Ionis)
Therapeutic Area:		spinal muscular atrophy
Patents/Generic Threats:		2030 U.S./2031 EU
2024 Sales:	Morningstar	$1.4 billion
	Consensus	$1.7 billion
Market Model:		—

While SMA drug Spinraza continues to grow strongly, particularly outside the U.S. and among older patients, we assume sales begin to decline in 2020 due to competition. Early positive data from Biogen's pivotal study in infants and priority review allowed Biogen to file for and receive FDA approval in 2016. Given the very high unmet need in this rare-disease market, sales have already reached $2.1 billion annually (2019). Novartis' gene therapy Zolgensma was approved in the U.S. in May 2019 in patients under the age of 2 (and in 2020 in Europe and Japan), which we think is making it more difficult for Biogen to gain newly diagnosed patients in this setting (60% of new cases are type 1, but infants are only 5% of the total SMA market). Roche/PTC's oral SMN2 splicing modifier, risdiplam had solid data from Sunfish and Firefish studies, and we believe pricing is likely to be competitive (Aug 2020 PDUFA, likely approval for types 1-3). However, Biogen treats 10,000 patients out of a total of 45,000 SMA patients in Biogen's markets, and rising prevalence (as more patients are treated) should help slow Spinraza declines. In addition, the high dose of Novartis' Strong study (intrathecal administration in type 2 patients) is on a partial clinical hold due to concerning preclinical side effects (inflammation and neuronal cell body degeneration or loss) with this route of administration, which could delay Zolgensma's approval in older children (Novartis still hopes to file in 2020). Spinraza data from the presymptomatic Nurture study show that the drug was able to keep patients near normal levels on the CHOP INTEND scale over a two-year period, with 96% able to walk with assistance after more than three years (June 2020 data update), likely due to earlier treatment, which could also prevent large-scale erosion of sales. The Devote trial, testing a higher dose of Spinraza (28mg every four months maintenance dose), began enrolling patients in April 2020, with the hope of further improving efficacy (data expected 2022).

Product:		Tysabri
Composition:		biologic (antibody)
Economics:		18%-25% royalty to Royalty Pharma
Therapeutic Area:		MS
Patents/Generic Threats:		2020-23, U.S./EU
2024 Sales:	Morningstar	$1.9 billion
	Consensus	$1.6 billion
Market Model:		MS (p.177)

Tysabri's improving safety profile and strong efficacy position it well in the moderate to severe MS niche, and we don't have any biosimilar threats on our radar. However, new IV competition (Ocrevus) is preventing growth in MS, particularly as Tysabri failed in a progressive MS study in 2015 (Ocrevus is approved in this indication), and 30% of Tysabri patients were JC-virus positive ahead of the Ocrevus launch (which puts them at a higher risk of deadly side effect PML). While the phase 2 Action 2 study in stroke failed in 2018, and the phase 2 Opus study in drug-resistant epilepsy failed in 2020, Biogen is also studying every-six-weeks dosing in MS as part of an effort to improve safety with extended interval dosing, with more data (versus standard monthly dosing) likely available in 2021.

Product:		Ocrevus (ocrelizumab)
Composition:		biologic
Economics:		13%-24% U.S. royalties (from Roche)
Therapeutic Area:		MS
Launch Year/Probability:		U.S./Europe 2025+
2024 Sales:	Morningstar	$1.3 billion ($7.1 billion Roche sales)
	Consensus	$1 billion
Market Model:		MS (p.177)

Ocrelizumab's superior efficacy on relapses and disability versus Rebif, strong safety profile, and efficacy in primary progressive disease in phase 3 bode well for uptake, and twice-yearly IV looks convenient; we assume peak sales around $9 billion given the drug's 40% share of new and switch patients in the U.S. The U.S. launch has performed strongly since second quarter 2017, with both primary progressive and relapsing/remitting patients initiating therapy, and patients are switching from a variety of approved MS therapies. Ocrevus gained approval in Europe in January 2018. Novartis/Genmab's ofatumumab generated solid phase 3 data in RRMS in 2019 similar to that of Ocrevus and could compete (PDUFA September 2020), although Ocrevus likely has significant entrenchment with doctors, and existing Ocrevus patients could be hesitant to switch. Subcu administration for ofatumumab could be an advantage, although some patients may prefer to align treatments with twice-yearly doctor visits. That said, Ocrevus infusion time is falling from 3.5 hours to 2 hours with a new dosing schedule in 2020, and Roche is also moving forward with testing a subcu version of Ocrevus.

Product:		Benepali (Enbrel biosimilar)
Composition:		biologic (anti-TNF antibody)
Economics:		BIIB has EU rights (50/50 split with Samsung)
Therapeutic Area:		immunology
Patents/Generic Threats:		approved EU 2016 (biosimilar)
2024 Sales:	Morningstar	$550 million
	Consensus	$600 million
Market Model:		—

Biogen launched the first Enbrel biosimilar in Europe following a January 2016 approval, giving it better positioning than Flixabi. Early uptake has been stronger than for the first Remicade biosimilar, with preference for the biosimilar device over the branded version. Biogen is the market leader in Denmark, the U.K., and Norway and has over 40% volume share in Germany, Italy, and Sweden.

Product:		Flixabi (Remicade biosimilar)
Composition:		biologic (anti-TNF antibody)
Economics:		BIIB has EU rights (50/50 split with Samsung)
Therapeutic Area:		immunology
Patents/Generic Threats:		approved 2016 EU (biosimilar)
2024 Sales:	Morningstar	$150 million
	Consensus	$150 million
Market Model:		—

Biogen has a strong position in the more than $9 billion European market for TNF antibodies, but Flixabi's May 2016 approval puts it well behind Pfizer/Celltrion's Inflectra/Remsima.

Product:		Imraldi (Humira biosimilar)
Composition:		biologic (anti-TNF antibody)
Economics:		BIIB reports EU sales (50/50 profit split with Samsung)
Therapeutic Area:		immunology
Patents/Generic Threats:		approved 2017 EU (biosimilar)
2024 Sales:	Morningstar	$350 million
	Consensus	$500 million
Market Model:		—

Biogen's Imraldi approval makes it the only firm with biosimilars of all three top anti-TNF products in Europe. The drug launched in October 2018 with several other Humira biosimilar competitors (following patent expiration and settlement terms), and has a similar formulation to branded Humira, but an innovative device. We expect gradual uptake via tender markets at highly discounted prices, but the opportunity is substantial, as branded Humira had roughly $4 billion in sales in Europe prior to biosimilar launches.

Product:		Vumerity (diroximel fumarate)
Composition:		small molecule
Economics:		midteens royalties to Alkermes
Therapeutic Area:		MS
Patents/Generic Threats:		2033 U.S.
2024 Sales:	Morningstar	$550 million
	Consensus	$500 million
Market Model:		MS (p.177)

Alkermes filed an NDA for Vumerity in December 2018 under the 505 (b)(2) pathway, using safety data from the phase 3 EVOLVE-MS-1 study, and the drug received FDA approval in Oct 2019. A head-to-head five-week study, EVOLVE-MS-2, compared Vumerity to Tecfidera with the goal of showing differentiated gastrointestinal tolerability; data were presented in Nov 2019 showing shorter duration, severity, and daily impact of five key GI symptoms with Vumerity versus Tecfidera, with lower discontinuations due to GI adverse events (0.8% versus 4.8%). Because Tecfidera side effects fade with time, we don't expect significant numbers of current patients to switch to Vumerity, and we do expect oral competition from Bristol (Zeposia approved March 2020), J&J (ponesimod March 2020 filing), and Merck KGaA (Mavenclad approved 2019). Development outside the U.S. is still under consideration.

Moat Trend and Product Pipeline

Product:		aducanumab (BIIB037)
Composition:		biologic (beta amyloid antibody)
Economics:		Neurimmune (~10% royalties), partnership w/Eisai (Biogen keeps 55%/68%/20% of profits, U.S./Europe/Japan)
Therapeutic Area:		Alzheimer's disease
Launch Year/Probability:		2021/40%
2024 Sales:	Morningstar	$1.8 billion
	Consensus	$2.5 billion
Market Model:		Alzheimer's (p.180)

Aducanumab's development program has been a rollercoaster, and we currently model a 40% probability of approval and $3 billion in probability-weighted sales by 2029, with approval possible in 2021 (Biogen filed with the FDA in July 2020). We still see uncertainty around whether the FDA will see the weaker Engage trial as confirmatory of the benefit seen in the Emerge study. Trial terminations created a dataset with only 55% of the potential full 18-month data, as well as a significant dose interruption that will prevent clear data on long-term benefits to these patients even with re-dosing, and the FDA could require another trial. We first saw positive phase 1 cognitive benefit data at the highest dose in 2015, closely followed by the start of two phase 3 studies. However, these trials were halted in March 2019, as a futility analysis of pooled data from the two trials indicated that there was less than a 20% probability of meeting the primary endpoint. Then in October 2019, Biogen disclosed that one trial, Emerge, actually met its primary and secondary endpoints (reducing cognitive decline) at the high dose level, with data from additional patients, while Engage did not (22% slower decline in CDR-SB for high-dose patients than placebo in Emerge, and a 2% faster decline than placebo in Engage). Biogen believes Engage data was adversely impacted by earlier enrollment at lower doses, prior to protocol amendments, as analysis of patients who received high doses post-amendment showed similar efficacy (30% reduction in decline in CDR-SB in Emerge, 27% in Engage). We're encouraged by safety of dose titration to limit the ARIA side effect. Overall, we think trial design (amyloid-positive PET scans required, very early-stage patients, dose titration) and drug design (from healthy elderly antibodies) boost probability of approval, despite Eli Lilly's solanezumab failure in 2016. If the amyloid theory is indeed still viable, we could see competition from Roche, as gantenerumab's continuing phase 3 program should have interim data in 2021. Eli Lilly's high-dose solanezumab should have prevention data in patients with high amyloid levels but no memory symptoms (A4 study) in 2022. Eli Lilly could also have mid-stage data for N3pG-amyloid beta drug donanemab and tau-targeting zagotenemab in 2020-21.

		opinicumab (BIIB033)
Product:		
Composition:		biologic (LINGO antibody)
Economics:		—
Therapeutic Area:		MS
Launch Year/Probability:		2021/30%
2024 Sales:	Morningstar	$350 million
	Consensus	$100 million
Market Model:		MS (p.177)

This novel anti-LINGO program could be a multi-billion-dollar opportunity if the drug helps MS patients remyelinate nerve fibers and regain function, but proof-of-concept data in optic neuritis was mixed, and the phase 2 MS Synergy trial failed to meet its endpoints. That said, Biogen saw a signal in younger, earlier-stage RRMS patients in Synergy and has moved forward with the phase 2b Affinity study in 2017 (data mid-2020), targeting a subsegment of about 25% of MS patients. Opicinumab would be used as an add-on therapy to reverse pre-existing disability. We would expect an additional trial before regulatory approval. Based on successful MRI screening in the Affinity study, Biogen plans to re-enter development with oral remyelinating agent BIIB061, which is poised to enter a phase 2 study in combination with interferon-beta in 2020.

Product:		Timrepigene emparvovec / BIIB111/ NSR-REP1
Composition:		biologic (AAV2 gene therapy)
Economics:		—
Therapeutic Area:		choroideremia
Launch Year/Probability:		2021/60%
2024 Sales:	Morningstar	$250 million
	Consensus	$150 million
Market Model:		—

Biogen acquired this gene therapy as part of the $800 million Nightstar acquisition in June 2019, and phase 3 enrollment in the Star study completed in Nov 2019 in choroideremia, an X-linked inherited retinal disorder that leads to blindness. The treatment is comprised of an AAV2 vector containing the CHM gene for enzyme REP1, administered by subretinal injection. In Phase 1/2 studies, more than 90% of patients maintained visual acuity over two years. Biogen expects phase 3 data by the end of 2020. Roughly 15,000 patients exist in the G7, with 30-40% eligible for treatment. Biogen leads in this field, although Roche could eventually compete with two therapies, including Spark's phase 1/2 AAV2 gene therapy SPK-7001 (did not show a statistically significant benefit in recently enrolled patients as of Jan 2019, and there have been some issues with subretinal injections) and 4DMT's intravitreal 4D-110 (avoids complex subretinal injections, entering phase 1 in 2020).

Product:		Tofersen/BIIB067 (IONIS-SOD1)
Composition:		antisense oligonucleotide
Economics:		Low to mid-teens royalties to Ionis
Therapeutic Area:		ALS
Launch Year/Probability:		2022/30%
2024 Sales:	Morningstar	$150 million
	Consensus	$150 million
Market Model:		—

BIIB067 is targeted to SOD1 mutations in familial ALS, accounting for roughly 2% of ALS cases (more than 1,000 diagnosed). Positive phase 1 data at AAN 2019 showed significant lowering of SOD1 in the cerebrospinal fluid at three months at the highest tested dose of 100mg in 10 patients, and also a trend to slowing of clinical decline relative to placebo as measured by the ALSFRS-R. Pivotal trial VALOR should produce data in 2021. BIIB078 is also in phase 1 testing in ALS (it targets the C9orf72 mutation, accounting for 4% of cases, and should have data in 2021), and Biogen and Ionis are moving additional therapies for familial and sporadic (nonfamilial) forms of ALS into testing. The initiation of a study of ataxin-2-targeting ION541 in sporadic ALS (which could address more than 75% of the broader ALS population) is set for 2H 2020. Biogen has also independently moved forward with XPO1 inhibitor BIIB100, from Karyopharm, in sporadic ALS, and should have phase 1 data in 2020.

Product:		Cirara/BIIB093 (glibenclamide)
Composition:		IV small molecule (sulfonylurea)
Economics:		Remedy milestones/royalties
Therapeutic Area:		large hemispheric infarction
Launch Year/Probability:		2023/40%
2024 Sales:	Morningstar	$250 million
	Consensus	$200 million
Market Model:		$150 million

Acquired from Remedy, BIIB093 entered the phase 3 Charm study in August 2018 in this severe subset of ischemic stroke, which targets 15% of the 1.7 million ischemic strokes in the U.S., Europe, and Japan each year. The drug blocks SUR1-TRPM4 channels and reduces brain swelling, disability, and risk of death in earlier clinical studies. The drug is a reformulation of an oral diabetes drug. Data was expected in 2021, although Biogen noted that this could be delayed due to the acute hospital setting and pandemic-related trial delays. Biogen also has TMS-007 in a phase 2 study in acute ischemic stroke (potential best-in-class thrombolytic with extended treatment window), with data expected by the end of 2020.

Product:		Cinpanemab/BIIB054
Composition:		biologic (anti-synuclein antibody)
Economics:		Neurimmune
Therapeutic Area:		Parkinson's disease
Launch Year/Probability:		2023/20%
2024 Sales:	Morningstar	$300 million
	Consensus	no estimate
Market Model:		—

Cinpanemab blocks cell-cell transmission of aggregates by picking up alpha-synuclein seeds. The drug is in a large phase 2 study poised to produce safety and pharmacodynamics data by 2H 2020. Biogen is competing in the synuclein space with Roche's prasinezumab (Prothena program poised to generate outcomes data in 2020) and AbbVie (BioArctic's ABBV-0805 should have phase 1 data in 2021). Biogen also has a phase 1 trial of BIIB094 ongoing in Parkinson's, in partnership with Ionis, based on LRRK2 gain of function mutations.

Product:		BAN2401
Composition:		biologic (beta amyloid antibody)
Economics:		50/50 partnership (Eisai)
Therapeutic Area:		Alzheimer's disease
Launch Year/Probability:		2023/not included
2024 Sales:	Morningstar	no estimate
	Consensus	$50 million
Market Model:		Alzheimer's (p.180)

While we're bullish on the ability of BAN2401 to shrink plaques and slow cognitive decline, similar to aducanumab, uncertainty around the amyloid theory remains quite high, and our amyloid model for Biogen focuses on aducanumab. Eisai moved BAN2401 to phase 3 study Clarity AD in 2019, with data expected in 2022. Eisai and Biogen have a broad Alzheimer's partnership that includes BAN2401, which Eisai originally licensed from BioArctic. The phase 2 study of BAN2401 had strong efficacy data at the highest dose, with a significant slowing in decline as measured by ADCOMS (30% slower decline) and ADAS-Cog (47% slower decline) versus placebo, and a trend to a benefit on CDR-SB (26% slower decline). Detailed analysis presented in October 2018 included a subgroup analysis that seemed to indicate that this strong efficacy was not driven by fewer patients with APOE4 genetic variants in the highest-dose arm (30% of patients) than in the placebo arm (70% of patients). We're encouraged by the directionally positive data for the second-highest-dose group, which had an even higher proportion of APOE4-positive patients than the placebo group (90%) yet still saw positive trends on clinical decline. However, the data was confusing, as clinical endpoint data suggested that APOE4 carriers could actually be responding better to treatment than noncarriers, which would be puzzling, as carrier status was not a factor for clinical responses in the aducanumab phase 1 PRIME study. In addition, high-dose BAN2401 patients in the noncarrier group appeared to do slightly worse than placebo on CDR-SB, which is the chosen primary endpoint for Biogen's phase 3 studies of aducanumab. We think the small sample size for the analysis and variability in clinical endpoint data (which is largely based on questionnaires) make subgroup analysis difficult. We're inclined to put more reliance on the similar reductions in plaque levels (a much more objective, quantitative measure) for carriers and noncarriers in the BAN2401 high-dose arm.

Product:		Gosuranemab/BIIB092
Composition:		biologic (anti-tau antibody)
Economics:		—
Therapeutic Area:		Alzheimer's disease
Launch Year/Probability:		2024/not included
2024 Sales:	Morningstar	no estimate
	Consensus	no estimate
Market Model:		Alzheimer's (p.180)

Acquired from Bristol, BIIB092 failed in a phase 2 study in progressive supranuclear palsy but remains in a phase 2 Alzheimer's study (which began in May 2018 and should produce data in 2021). We think the drug could prove complementary to aducanumab in Alzheimer's in the long run. However, Biogen could see competition from AbbVie, whose ABBV-8E12 also failed in PSP and continues in Alzheimer's (data expected in 2021). Roche and AC Immune have a phase 2 tau antibody, semorinemab/RG-6100, that should generate data in 2020-21. Eli Lilly's ACI-3024, a tau inhibitor small molecule from AC Immune, entered phase 1 in 2019. Partner Eisai also has a competing tau antibody, E2814, which entered a study in healthy volunteers in late 2019. Biogen has other tau-targeted drugs in development, including BIIB076 (from Neurimmune, with phase 1 Alzheimer's data expected in 2020) and IONIS-MAPTRx/BIIB080 (from Ionis, phase 1/2 Alzheimer's data in 2022), which we do not explicitly model.

Product:		BIIB112/NSR-RPGR
Composition:		biologic (AAV2 gene therapy)
Economics:		—
Therapeutic Area:		X-linked retinitis pigmentosa
Launch Year/Probability:		2024/50%
2024 Sales:	Morningstar	$100 million
	Consensus	$60 million
Market Model:		—

Biogen's other Nightstar ophthalmological gene therapy program, BIIB112/NSR-RPGR, is for XLRP, a form of night blindness in children that progresses to legal blindness by the early 40s. BIIB112 could target 20,000 patients in the G7, with phase 2/3 data expected by mid-2021. Initial phase 1 dose-escalation data published in Feb 2020 showed solid safety, and sustained vision improvements in six of the 18 patients studied. Another trial will be required for approval, however. AGTC's AGTC-501 (enrolled two highest dose groups in phase 1/2 in Feb 2020, to start pivotal trial in 2020) and MeiraGTx/J&J (AAV-RPGR in phase 1/2, data 2020E) could be on similar timelines to approval.

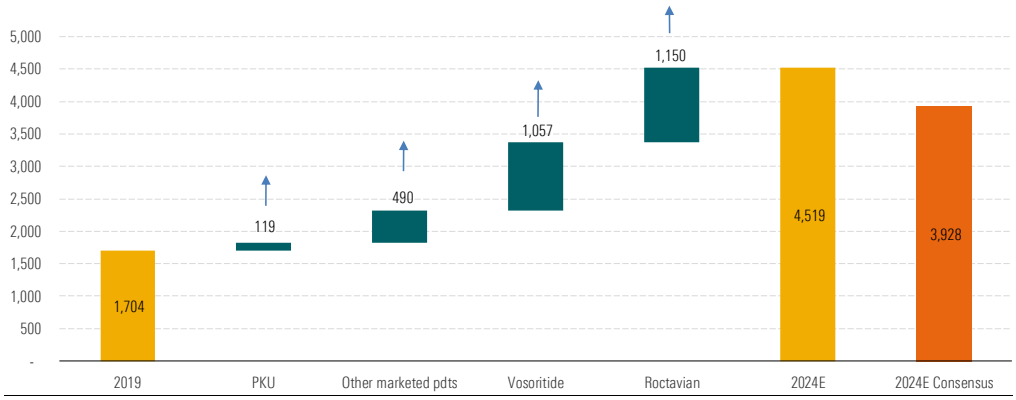
Product:		BIIB059
Composition:		biologic (BDCA2 antibody)
Economics:		—
Therapeutic Area:		Lupus (CLE, SLE)
Launch Year/Probability:		2024/30%
2024 Sales:	Morningstar	$200 million
	Consensus	no estimate
Market Model:		—

Biogen's phase 2 Lilac study reported out in Dec 2019, with details at EULAR 2020. The cutaneous lupus erythematosus (CLE) portion saw 39-48% reductions in CLASI-A scores at week 16 (14.5% placebo), showing lower disease activity. The systemic lupus erythematosus (SLE) portion saw total active joint count at week 24 reduced by 3.4 at the highest dose relative to placebo. Biogen is planning to move to phase 3 in 2020. The drug could compete with Astra's anifrolumab, which saw positive data in the Tulip-2 study in 2019. Biogen/UCB's dapirolizumab pegol (CD40L) failed in phase 2b in 2018, but Biogen announced in 2019 its plans to move to phase 3 in 2020, as despite the miss, it hit most clinical endpoints. However, we do not model the UCB drug in our Biogen valuation.

BioMarin BMRN

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$119.00	1.07	Medium	Narrow	Positive

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst, Visible Alpha for consensus.

Beyond Kuvan, BioMarin's Portfolio and Pipeline Have Long-Term Growth Potential

Expiring Patents

Most of BioMarin's products have peak market potential below $1 billion and are difficult to manufacture, making them less appealing targets for biosimilar makers, despite expiring patents. In addition, biosimilar makers would see a challenge in converting established patients to a new therapy on a global level, particularly given the wide dispersion of patients. BioMarin's only key small-molecule drug, Kuvan, will see at least two generics enter the U.S. market in 2020.

Inline Products

BioMarin has an exclusive focus on rare diseases, particularly forms of skeletal dysplasia (Aldurazyme, Naglazyme, Vimizim, and vosoritide) as well as rare metabolic disorders like PKU (Kuvan, Palynziq). Its enzyme-replacement therapies help the firm derive strong competitive advantages, high pricing power, and a narrow moat. Brineura (2017 launch) should slowly ramp as prevalence grows with treatment, and Palynziq (2018 launch) should protect BioMarin's PKU franchise from declines despite Kuvan's patent expiration.

Pipeline

BioMarin is capable of launching two products with more than $1 billion in peak sales potential through 2021, including hemophilia A gene therapy Roctavian (H2 2020) and achondroplasia treatment vosoritide (2021), and our forecasts are above consensus for both products. BioMarin has other programs—including PKU gene therapy—in earlier development.

Moat and Product Portfolio

Expiring Patents

Product:		Kuvan (sapropterin)
Composition:		small molecule (BH4 cofactor)
Economics:		in-house (Japan royalty from Daiichi Sankyo)
Therapeutic Area:		mild/moderate phenylketonuria
Patents/Generic Threats:		2020 U.S. (Dr. Reddy's/Par settlements) 2024 EU (exclusivity)
2024 Sales:	Morningstar	$200 million
	Consensus	$150 million
Market Model:		—

Kuvan controls phenylalanine levels and provides cognitive benefits in 30%-50% of PKU patients and has built a strong sales base in the U.S., particularly among children (who are typically on restricted diets as their only other treatment). Settlements with Dr. Reddy's and Par will allow U.S. generic entry in October 2020. We expect continued growth through 2020 in the U.S. as additional pediatric patients initiate therapy, but uptake could grow outside the U.S. through 2024 (although Kuvan is only used in adults ex-U.S., and Palynziq's launch is likely to compete here). BioMarin acquired ex-U.S. rights to the drug from partner Merck KGaA in 2016 and is prioritizing awareness, as only 500 of the roughly 5,000 patients seen at a clinic are taking Kuvan. Censa (being acquired by PTC) is working on an oral BH4 precursor CNSA-001 (better Phe reduction than Kuvan in a phase 2 study in Dec 2019), and Synlogic has a probiotic SYNB1618 (phase 1/2a data in Sept 2019, phase 2 start likely in 2020), but neither should affect Kuvan sales prior to generics.

Inline Products

Product:		Aldurazyme (laronidase)
Composition:		biologic (enzyme replacement)
Economics:		50/50, Sanofi
Therapeutic Area:		MPS I
Patents/Generic Threats:		2020 U.S.
2024 Sales:	Morningstar	$100 million
	Consensus	$100 million
Market Model:		—

BioMarin's first marketed rare-disease product, for a form of skeletal dysplasia, is maturing, with slower growth potential than the rest of the firm's portfolio. Gene therapy could eventually compete (Regenxbio's RGX-111 is in phase 1/2). Sangamo's ZFN gene editing drug had weak efficacy in an early-stage study in Feb 2019, and the firm is moving to potentially more potent next-generation versions.

Product:		Naglazyme (galsulfase)
Composition:		biologic (enzyme replacement)
Economics:		—
Therapeutic Area:		MPS VI
Patents/Generic Threats:		2023 U.S.
2024 Sales:	Morningstar	$425 million
	Consensus	$450 million
Market Model:		—

Naglazyme treats a rare form of skeletal dysplasia. It continues to see solid uptake, particularly in new markets outside the U.S. and Europe, although reliance on tender markets in South America add volatility to quarterly results. As market penetration increases, additional growth is likely to come from growing patients (the drug is dosed per kilogram of body weight), not from price increases (prices are high but remain flat globally).

Product:		Vimizim (GALNS)
Composition:		biologic (enzyme replacement)
Economics:		—
Therapeutic Area:		Morquio A syndrome, MPS IVA
Patents/Generic Threats:		2029 U.S./2024 EU
2024 Sales:	Morningstar	$800 million
	Consensus	$750 million
Market Model:		—

Vimizim has larger sales potential than most of BioMarin's other enzyme replacement therapies, due to a large identified patient population. More than 2,100 globally have been diagnosed, and there are likely 3,000 patients with the disease globally with no alternative therapies. Launched in 2014, the drug is still growing well as it penetrates the market.

Product:		Palynziq/pegvaliase (PEG-PAL)
Composition:		biologic (bacterial enzyme)
Economics:		—
Therapeutic Area:		PKU (classic)
Patents/Generic Threats:		Patents 2028 (2030 exclusivity)
2024 Sales:	Morningstar	$450 million
	Consensus	$650 million
Market Model:		—

While Kuvan is approved to treat patients with a milder form of PKU, Palynziq's strong efficacy allows adult patients to liberalize their diets with treatment. Peak sales of $700 million for BioMarin's PKU franchise (including Kuvan) looks feasible and more than $500 million for Palynziq alone, given the dramatic Phe lowering and lack of other treatment options, despite the fact that approval will likely be limited to adults for the foreseeable future (managing safety and titrating dosing in children would be more burdensome). We caution that the launch will take time, as the limited number of PKU clinics and individual patient dose titration means that initial drug costs are substantially lower than the $192,000 net cost of maintenance treatment (with the exception of the 200 clinical trial patients who are converting to commercial drug). Palynziq was approved in the U.S. in May 2018 (European approval in May 2019) and should boost sales among adult PKU patients, as only 12% of U.S. patients received Kuvan (roughly 40% of Palynziq patients were previously on Kuvan). BioMarin is also starting a phase 1/2 study for PKU gene therapy BMN-307 in 2H 2020 (at commercial manufacturing scale), which should allow BioMarin to remain dominant in PKU despite potential competition. In small molecules, BMN-307 could compete with PTC/Censa (see Kuvan section). In gene therapy, BMN-307 could compete with Homology Medicines; gene therapy HMI-102 had phase ½ data in December 2019 showing positive data in one patient in cohort 2, with Phe levels 48% lower at week 4 (low dose patients in cohort 1 did not have a response). However, Homology does not have a track record in gene therapy manufacturing.

Product:		Brineura/cerliponase alfa (BMN-190)
Composition:		biologic (TPP1 enzyme)
Economics:		—
Therapeutic Area:		CLN2 disease (Batten disease)
Patents/Generic Threats:		2028 U.S./2028 EU
2024 Sales:	Morningstar	$250 million
	Consensus	$250 million
Market Model:		—

Data in early 2015 showed potential for stabilizing this severe neurological disorder, and 48-week data in early 2016 showed an impressive ability to stabilize 65% of patients for the full year of treatment. BioMarin filed on this phase 1 data in just 24 patients in 2016, and due to the severity of this neurodegenerative disorder (most children can no longer walk or talk by age 6) regulators approved the drug in April 2017. European reimbursement expanded over the course of 2018. Early diagnosis remains a hurdle to rapid uptake; there are roughly 1,500 patients worldwide with this disease, but only one third are found early enough in the disease to qualify for treatment. As treatment rates climb, prevalence should approach that of MPS I and MPS IVA, at roughly 3,000 globally (average net price is $486,000 annually). We assume sales surpassing $300 million by the end of our 10-year forecast. Gene therapy competition from Regenxbio is still preclinical.

Moat Trend and Product Pipeline

Product:		Roctavian (valoctocogene roxaparvovec, BMN-270)
Composition:		biologic (AAV, BDD-factor VIII gene therapy)
Economics:		—
Therapeutic Area:		hemophilia A
Launch Year/Probability:		2020/70%
2024 Sales:	Morningstar	$1.1 billion
	Consensus	$750 million
Market Model:		hemophilia (p.173)

We expect a 2020 launch (August 2020 PDUFA, early 2021E Europe approval) and peak sales north of $1 billion for Roctavian, which is the leading hemophilia A gene therapy in testing. BioMarin began pivotal trials in the fourth quarter of 2017 and has completed enrollment in the 301 study, with full one-year data expected in Q1 2021. This superiority study includes 130 patients and pits Roctavian against prophylaxis therapy. The FDA accepted BioMarin's filing based on factor 8 levels in a portion of patients in the high-dose phase 3 study (where the drug led to normal range levels between 6 and 12 months after administration), as well as three-year data from the phase 1/2 study. The key unknown is the durability of Roctavian's effects on factor 8, as there was a slight decline at two years and again at three and four years in the initial phase 1/2 study that began in 2015, after the therapy was licensed from University College London. However, we were reassured by factor VIII level declines that are slowing since year two. We think BioMarin's significant lead over Roche/Spark (SPK-8011 entering phase 3 in 2021) and Pfizer/Sangamo (SB-525, to start phase 3 dosing 2H 2020) and likely Roctavian efficacy for eight years or longer support our assumption of $1.3 billion in peak sales. This assumes a global net price around $1.2 million per patient (closer to $2 million in the U.S.), and market share (of non-cured severe hemophilia adults and adolescents) rising as high as 7% annually. While not included in our model, BioMarin expects to expand usage gradually to include patients with AAV5 antibodies as well as younger patients (adolescents) and patients with milder disease (up to 70,000 total). BioMarin is treating patients without the use of steroids (liver enzyme elevations look manageable), and manufacturing looks stable. BioMarin began gene therapy manufacturing at a large, in-house facility as of spring 2018, and is capable of treating 10,000 gene therapy patients annually, making manufacturing expertise a competitive advantage and allow gene therapy to become a potential new platform for the firm. BioMarin is initially targeting adult patients with severe hemophilia, and 80% of U.S. candidates should be eligible for treatment based on lack of pre-existing AAV5 immunity (a companion diagnostic from ARUP Laboratories will be launched with the treatment). We estimate roughly 30,000 eligible patients in developed markets.

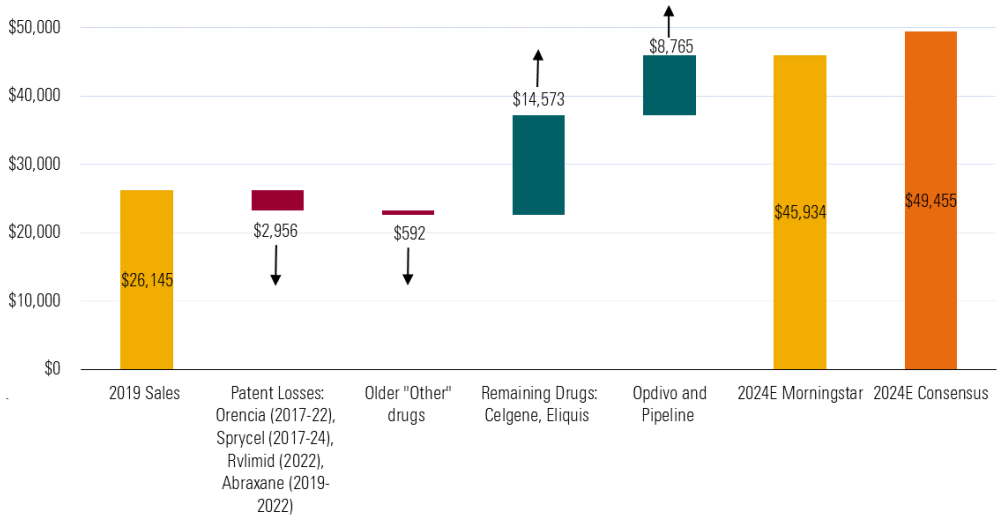
Product:		vosoritide (BMN-111)
Composition:		biologic (C-type natriuretic peptide analog)
Economics:		—
Therapeutic Area:		achondroplasia
Launch Year/Probability:		2021/90%
2024 Sales:	Morningstar	$1.1 billion
	Consensus	$550 million
Market Model:		—

We think vosoritide could be among the largest pipeline opportunities for BioMarin, with more than $1 billion in peak sales assuming a $150,000 price tag and patent protection through 2030. There are roughly 22,000 patients eligible for treatment in BioMarin territories, corresponding to the one-fourth of achondroplasia patients who still have open growth plates. A once-daily, 15 ug subcutaneous dose of the drug is able to restore growth rates to normal levels among patients with the most common form of dwarfism, and we expect BioMarin to file for approval in the U.S. and Europe in 3Q 2020. In December 2019, BioMarin announced that vosoritide passed a key phase 3 data hurdle, as patients over the age of 5 taking the drug for one year grew an additional 1.6 centimeters over patients on placebo, which is roughly consistent with recent phase 2 data showing 9 centimeters in cumulative additional growth for vosoritide patients over 54 months beyond historical comparisons. BioMarin is also testing vosoritide in children under the age of 5, and we expect safety data from these studies to potentially allow the FDA to give the drug a broad initial approval in 2021. While the drug may also improve proportionality in these patients, we don't expect conclusive data here for several years and expect regulators to approve the drug--which has a strong safety profile--based on growth velocity results, as an advisory committee meeting in 2018 on achondroplasia drug development agreed this would be an appropriate primary endpoint. BioMarin also plans to start a study in dominantly inherited short stature (DISS) in H2 2020. Two competitors are in earlier-stage testing and aiming for an improved, once-weekly dosing profile, but data is minimal. Phase 1 data for Ascendis' TransCon CNP in healthy volunteers in November 2018 showed viability of once-weekly subcutaneous dose and the drug entered phase 2 in achondroplasia in third-quarter 2019. Therachon's FGFR3 decoy drug TA-46 generated phase 1 proof of concept data in healthy volunteers, and Pfizer paid $340 million upfront to acquire Therachon in 2019; phase 2 in patients up to 10 years of age should start in 2020.

Bristol-Myers Squibb BMY

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$68.00	0.89	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst/S&P Cap IQ for consensus.

Opdivo Still Offers Some Growth Potential Despite Setbacks, but Pipeline and Eliquis are Drivers

Expiring Patents

Bristol's acquisition of Celgene brings in major approaching patent losses with Revlimid (starting in 2022) along with Abraxane (2019-2022). Also, we expect biosimilar pressures on immunology drug Orencia by 2022 as well as generics on cancer drug Sprycel by 2024 in the U.S.

Inline Products

Opdivo still holds some potential in renal, lung and skin cancers, but Merck's strong competitive positioning of Keytruda will likely slow Opdivo's gains. Eliquis remain in the best position in atrial fibrillation, but the market share gains will likely slow as the drug is saturating the market.

Pipeline

Outside the TYK2 drug BMS-986165 for psoriasis, the majority of Bristol's late-stage pipeline was gained through the Celgene acquisition. Zeposia/ozanimod (multiple sclerosis and bowel disease), liso-cel (cancer), and bb2121 (cancer) all look well positioned for significant gains.

Moat and Product Portfolio

Expiring Patents

Product:		Sprycel
Composition:		small molecule (Bcr-Abl)
Economics:		small royalty to Otsuka
Therapeutic Area:		CML
Patents/Generic Threats:		2020-24 U.S./2017-24 international
2024 Sales	Morningstar	$609 million
	Consensus	$756 million
Market Model:		—

Sprycel's differentiated mechanism of action, fewer food interactions, once-daily dosing, and strong efficacy (slightly worse data in reduction in blastic phase of CML versus Tasigna) should continue to support sales despite generic Gleevec competition that emerged in 2016.

Product:		Orencia
Composition:		biologic (T cells)
Economics:		joint partnership with Ono in Japan
Therapeutic Area:		Rheumatoid arthritis (RA)
Patents/Generic Threats:		2016 or later U.S./2017 international
2024 Sales	Morningstar	$1,962 million
	Consensus	$2,707 million
Market Model:		RA (p.167)

Orencia offers the only CTLA4 target in treating RA, and ACR guidelines continue to push the drug further up the treatment path, opening the door for easier competition for patients failing methotrexate. Additionally, in 2017, Momenta and Mylan announced that M834, an Orencia biosimilar, did not meet its primary pharmacokinetic endpoints in a phase I study, suggesting a high level of complexity in manufacturing the drug.

Product:		Revlimid (lenalidomide)
Composition:		small molecule (immunomodulator/IMiD)
Economics:		—
Therapeutic Area:		hematological oncology (multiple myeloma/MDS/follicular lymphoma)
Patents/Generic Threats:		2022 U.S. (settlements)/2022 EU
2024 Sales	Morningstar	$5,876 million
	Consensus	$7,917 million
Market Model:		multiple myeloma (p.188)

IMiD Revlimid should continue to see strong growth, ahead of Teva's U.S. generic launch in 2022. While patent protection until 2022 in Europe seems likely, the situation in the U.S. is more complicated. Celgene (now Bristol) settled with Natco (now Teva) in December 2015, paving the way for the launch of its generic Revlimid in the U.S. beginning in March 2022 on a limited basis. According to the terms, Teva can grow from a mid-single-digit percentage of volume that year up to a third of volume in 2025, and restrictions on competition will be lifted in February 2026.

Alvogen should also launch limited quantities beginning in 2022. Dr. Reddy's, Zydus, Cipla, Lotus, Apotex, and Sun have also filed ANDAs and could launch following their 30-month stays. While theoretically this implies a launch at any time, this would be an at-risk launch, and litigation and appeals are unlikely to be settled prior to 2022.

The SWOG S0777 study made a combination with Velcade the standard in the first-line nontransplant myeloma setting, boosting future duration of use (43-month PFS was achieved). Combination regimens with other novel drugs are also allowing patients to see better survival rates and stay on therapy longer; recent data from a first-line study with Darzalex (Maia) showed a 45% reduction in risk of progression or death compared with the control arm, which had a 31.9-month PFS (median PFS not reached for the Darzalex/Revlimid combination). Recent approval for Revlimid in the post-transplant setting further boosts long-term market share potential. In lymphoma, the Remarc and Relevance studies failed to improve on standards of care, but Augment (RR follicular lymphoma) showed impressive ability to extend PFS when combined with Rituxan.

Product:		Abraxane (protein-bound paclitaxel)
Composition:		small molecule (microtubule stabilizing drug)
Economics:		—
Therapeutic Area:		oncology (breast/lung/pancreatic)
Patents/Generic Threats:		2022 U.S. (settlements)/2019 EU (market exclusivity)
2024 Sales	Morningstar	$253 million
	Consensus	$591 million
Market Model:		—

Abraxane sales in breast cancer are relatively steady and launches in lung and pancreatic cancer have boosted growth, although competition from PD-1 antibodies used as monotherapy in lung cancer has put pressure on recent sales. IMpower 130 (nonsquamous NSCLC) and IMpassion 130 (triple-negative breast cancer) both had positive data in 2018 in combination with Roche's immuno-oncology therapy Tecentriq, which could provide a boost to sales. Abraxane has orphan exclusivity in pancreatic cancer in the U.S. until 2020, and Celgene settled with ANDA filers Teva, Apotex, and Cipla in 2018, allowing them to launch in the U.S. in 2022. In Europe, Bristol is fighting for supplemental protection that would extend patent protection to 2022, although as it stands now, data exclusivity expired in January 2019.

Inline Products

Product:		Eliquis
Composition:		small molecule (Factor Xa)
Economics:		~60% of profits to Pfizer
Therapeutic Area:		cardiovascular/AFib
Patents/Generic Threats:		2026 global
2024 Sales	Morningstar	$12,636 million
	Consensus	$12,375 million
Market Model:		atrial fibrillation (p.172)

Eliquis' superior data on stroke prevention, low bleeding rates, and mortality should drive leading share in atrial fibrillation and offset its late market entry. PFE/BMY's Eliquis should net 50%+ share in the $20 billion-plus market (up from 45% currently, twice-daily dosing, but with mortality benefit) versus Xarelto's once-daily dosing/first-mover advantage in AF, DVT/PE, and ACS (EU), which should net 30%+ share up from 25% currently at the expense of warfarin (20% market share currently). However, with no major studies ongoing for further Eliquis label expansion, we don't expect any acceleration in the drug's sales ramp.

Product:		Yervoy
Composition:		biologic (CTLA-4)
Economics:		internal (Medarex)
Therapeutic Area:		cancer
Patents/Generic Threats:		2023 U.S./2021 international
2024 Sales	Morningstar	$1,856 million
	Consensus	$2,041 million
Market Model:		—

Yervoy's main driver is its combination with Opdivo in melanoma and renal cancer (intermediate or poor risk). We expect expanded usage into other cancer indications—lung in particular, with positive data in Checkmate 227 and Checkmate 9LA—but lower dosing may moderate the potential in lung cancer.

Product:		Opdivo
Composition:		biologic (PD1)
Economics:		royalty to Ono (4% in North Am, ~15% in other applicable territories)
Therapeutic Area:		cancer
Patents/Generic Threats:		2027 U.S./2026 EU/2031 Japan
2024 Sales	Morningstar	$9,891 million
	Consensus	$9,563 million
Market Model:		immuno-oncology (p.181)

Despite setbacks in Checkmate 026 and 227 part 1, Opdivo is still well positioned to gain a major share of the immuno-oncology market due to a first mover advantage in renal cancer and melanoma and some entrenchment in lung cancer. We expect Bristol to gain 18% of the $53 billion immuno-oncology market by 2024. The keys going forward are adjuvant studies and combinations.

In 2020, key data includes CM227 part 1a (FDA approved in May 2020, but was rejected by Europe), CM9LA (lung, OS HR of 0.66 is not likely to take much share from Keytruda, FDA approved in May 2020 and maybe EU approval by year end as well), CM9ER (renal with cabozantinib, positive overall survival topline in April 2020), CM743 (mesothelioma, positive topline overall survival in April 2020), CM648 (additional esophageal data, but already approved in the U.S. in June 2020 on phase 3 Attraction data), CA224-047 (melanoma, plus LAG3 drug), CM274 (bladder adjuvant plus Yervoy), CM816 (lung, neo-adjuvant).

Later Opdivo+Yervoy studies:
Due in 2021: CM557 (esophageal adjuvant)
Due in 2022: CM901 (bladder), CM649 (gastric), CM743 (mesothelioma), CM914 (renal adjuvant), CM9ut (bladder adjuvant), CM9dx (liver, adjuvant) ANVIL (adjuvant lung)
Due in 2023: CM9dw (liver), CM7dx (prostate), CM73l (stage 3 lung), CM77T (peri lung), CA017-078 (bladder adjuvant)

Due in 2024: CM76k (melanoma stage 2b/c adjuvant)

Less optimistic outlook for the following studies:
CM915 (adjuvant melanoma, plus Yervoy) due in 2020, but initial data didn't show a benefit for patients with low levels of PDL1 expression
CM548 (brain, GBM) due in 2022-23, but PFS already read out negatively and other studies in this indication have not worked.
CM651 (Head and Neck) should have results in 2021 but a failure in a similar Phase 2 study (CM714) makes us less optimistic, plus Keytruda looks well positioned here.

Product:		Pomalyst (pomalidomide)
Composition:		small molecule (immunomodulator/IMiD)
Economics:		—
Therapeutic Area:		hematological oncology (multiple myeloma)
Patents/Generic Threats:		2025 U.S./2023 EU (orphan exclusivity)
2024 Sales	Morningstar	$3,527 million
	Consensus	$3,347 million
Market Model:		multiple myeloma (p.188)

Launched in 2013, Pomalyst's strong efficacy and lack of cross resistance with Revlimid make it a solid option for multiple myeloma patients with relapsed or refractory disease. Sales have grown as the drug has gained market share and longer durations in the third-line setting; recent approval in combination with Darzalex and studies with PD-1 antibodies in this setting could further boost duration. In addition, Celgene had strong data in combination with Velcade in the second-line setting (Optimismm) at ASCO 2018. We assume the U.S. 2025 substance/method of use patent holds (if not, several ANDA filers could launch in 2020), and we see orphan drug exclusivity as the strongest protection for the drug outside the U.S.

Product:		Inrebic/fedratinib
Composition:		small molecule (JAK2)
Economics:		—
Therapeutic Area:		myelofibrosis
Patents/Generic Threats:		
2024 Sales	Morningstar	$596 million
	Consensus	$361 million
Market Model:		—

Inrebic's efficacy in a subset of patients who aren't currently served well by Incyte's Jakafi could lead to $1 billion in sales out of a $2 billion myelofibrosis market. According to Celgene, 40% of myelofibrosis patients are either Jakafi failures or have a low platelet count and can't take Jakafi, with the remainder taking Jakafi. Eight cases of Wernicke's encephalopathy in fedratinib studies (out of 877 patients in Jakarta-2) appear unrelated to drug after further analysis; a clinical hold in 2013 led Sanofi to abandon the program, but the clinical hold was removed in August 2017.

Product:		Reblozyl/luspatercept (ACE-536)
Composition:		biologic (activin receptor fusion protein)
Economics:		co-promotion/profit share (Acceleron)
Therapeutic Area:		beta thalassemia, MDS
Patents/Generic Threats:		
2024 Sales	Morningstar	$885 million
	Consensus	$1,077 million
Market Model:		—

Luspatercept's phase 3 data in MDS (Medalist) and beta-thalassemia (Believe) was solid, and the drug appears to reduce anemia, transfusion burden, and iron overload for patients with these blood disorders. The FDA approved the drug for beta thalassemia in Nov. 2019 and for MDS in April 2020, followed by European approvals in June 2020. Assuming an addressable MDS/beta-thalassemia/myelofibrosis patient population of at least 120,000 in the U.S. and Europe, we think luspatercept could easily see peak sales of $2 billion, with pricing close to $170,000 annually and roughly 10% market penetration. Luspatercept sales could cannibalize Revlimid in MDS (approved in low-risk deletion 5q patients), and Bluebird stands out as a key competitor in beta-thalassemia (LentiGlobin/Zyntelgo gene therapy was approved in Europe in 2019 and is launching in 2020, and should be filed in the U.S. with additional data in 2021).

Moat Trend and Product Pipeline

Product:		Relatlimab
Composition:		biologic/Anti-LAG 3
Economics:		partnered with Ono
Therapeutic Area:		cancer
Launch Year/Probability:		2021/40%
2024 Sales	Morningstar	$375 million
	Consensus	$170 million
Market Model:		—

Lymphocyte activation gene 3 (LAG-3, CD223) is a checkpoint protein inhibitory receptor coexpressed with PD-1 on tolerant tumor infiltrating lymphocytes. LAG-3 is also expressed on regulatory T cells, and it suppresses antigen-presenting cell activation by binding with major histocompatibility complex II. In animal models, LAG-3 has demonstrated synergistic activity with other down-regulatory pathways, specifically PD-1 and TIM-3. While synergistic with PD-1/PD-L1, the LAG-3 target could also act as monotherapy. In an early-stage study with patients refractory to Yervoy and IO therapy, the drug combined with Opdivo showed an ORR of 12% (all) and 18% (LAG-3>1%). Several phase 2 studies in lung, gastric, renal, and skin cancer should report out during 2020-22. The first registrational data should come in late 2020 (047 study) in melanoma.

Product:		BMS-986165
Composition:		small molecule/TYK2
Economics:		—
Therapeutic Area:		immunology
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	$473 million
	Consensus	$53 million
Market Model:		psoriasis (p.166)

With an interesting mechanism of action in blocking receptors for IL-12, IL-23, and type I interferons, Bristol's TYK2 inhibitor could work well in immunology disease with a potential focus in psoriasis. Phase 2 data in mid-2018 showed PASI 75 rates as high as 74% in biologically experienced patients. Two phase 3 studies (POETYK) versus Otezla should complete in late-2020/early 2021. Additional indications should support more market potential with phase 2 data coming in psoriatic arthritis (2020), lupus (2021) and ulcerative colitis (2021).

Product:		NKTR-214
Composition:		biologic (peg-IL-2)
Economics:		Bristol paid $1.8B to Nektar for 35% of profits
Therapeutic Area:		cancer
Launch Year/Probability:		2022/50% in melanoma
2024 Sales	Morningstar	NA
	Consensus	NA
Market Model:		—

NKTR-214 is a natural killer stimulator in registrational studies for first-line melanoma (data in 2022), first-line renal cancer (data in 2021-22), first-line bladder cancer (data 2021), and second-line non-small-cell lung cancer (data TBA).

Product:		BMS-986177
Composition:		Small molecule (FXIa inh.)
Economics:		Share profits with J&J
Therapeutic Area:		cardiovascular
Launch Year/Probability:		2024/40%
2024 Sales	Morningstar	
	Consensus	
Market Model:		—

BMS-986177 is a small molecule Factor XIa inhibitor in development for stroke and venous thromboembolism prevention. Phase 2 studies should complete in 2021, setting a decision for phase 3 development.

Product:		Zeposia/ozanimod
Composition:		small molecule (S1P receptor, types 1 and 5)
Economics:		—
Therapeutic Area:		MS, ulcerative colitis, Crohn's disease
Launch Year/Probability:		2020/100% MS, 70% UC, 50% CD
2024 Sales	Morningstar	$1,634 million
	Consensus	$1,471 million
Market Model:		MS (p.177), Crohn's/UC (p.168)

The FDA approved Zeposia/Ozanimod in March 2020 (but launch was delayed due to the coronavirus), followed by European approval in May 2020 and the drug is in advanced development ulcerative colitis (phase 3 True North data reported positive topline data in June 2020), and Crohn's disease (phase 3 data 2020). Once-daily administration and potential for a differentiated cardiovascular profile versus Gilenya (which is less targeted) are encouraging for ozanimod's MS potential, but close-following competition from J&J's ponesimod (filed March 2020) and approval delays keep us at the low end of management's $4 billion-$6 billion peak sales guidance for the drug. The drug benefits from the failed 2018 IPR challenge to Gilenya, which could push generic Gilenya entry from 2019 to 2027.

October 2017 presentation of Sunbeam and Radiance phase 3 data in MS at ECTRIMS showed better reductions in relapse rates than Avonex but failed to show a benefit on disability progression versus Avonex. In Crohn's, efficacy also looked promising, as single-arm phase 2 Stepstone had a mean CDAI reduction at week 12 of 130 points, with 66% responding and 46% remission. Ozanimod's phase 2 UC data looked potentially better than Humira. Patent protection runs through the late 2020s. The drug is also one of three drugs part of the CVR with an approval needed by the end of 2020.

Product:		Liso-cel/JCAR017
Composition:		biologic (CD19 targeting cell therapy)
Economics:		—
Therapeutic Area:		DLBCL, CLL
Launch Year/Probability:		2020/75%
2024 Sales	Morningstar	$1,245 million
	Consensus	$835 million
Market Model:		NHL (p.185), CLL (p.187)

JCAR017 was filed with the FDA in mid-December 2019 for refractory non-Hodgkin's lymphoma and had a PDUFA date of Aug. 17, 2020, but was delayed to Nov. 16 due to the FDA asking for more information. Approval would make it potentially third to market among CD19-targeting CAR-T cell therapies. The program was part of an ex-U.S. collaboration with Juno and is now fully owned following the $9 billion Juno acquisition in 2018 by Celgene. JCAR017 has a different costimulatory antigen from Juno's previous lead CAR-T-cell therapy targeting CD19, JCAR015, (JCAR017 uses 4-1BB) and generated better safety data in the Transcend study. Among the 37 core DLBCL patients at dose level 2 in this study, liso-cel saw a 53% complete response rate with data at ASH 2019 (including no severe CRS and only 8% severe neurotoxicity). Data in CLL at ASH 2018 was impressive as well, with a 43% complete response rate after several lines of prior therapy. The competitive landscape is crowded, with Novartis' Kymriah approved in pediatric ALL in August 2017 and DLBCL in May 2018, and Gilead's Yescarta (KTE-C19) launched in DLBCL in late 2017. The drug is also one of three drugs part of the CVR with an approval needed by the end of 2020.

Product:		CC-486 (oral aza)
Composition:		small molecule
Economics:		—
Therapeutic Area:		Blood cancer MDS: Myelodysplastic syndromes AML: Acute myeloid leukemia
Launch Year/Probability:		2020/50%
2024 Sales	Morningstar	$1,051 million
	Consensus	$620 million
Market Model:		—

CC-486 could extend Vidaza sales, and the oral formulation could prove not only more convenient but also more effective due to longer exposure at lower levels than IV Vidaza. Phase 3 trials in AML maintenance looked strong at ASH 2019 with an OS HR of 0.69 and an 81% complete response rate. With close to 11,000 people dying from AML each year in the U.S., the population is small, but we would expect strong pricing to drive total sales over $1 billion. The drug was filed with the FDA in May 2020 and accepted for filing by Europe in May as well.

Product:		bb2121/bb21217
Composition:		cell therapy (CAR-T targeting BCMA)
Economics:		Bluebird Bio U.S. 50/50 profit share, Bristol controls ex U.S.
Therapeutic Area:		Relapsed multiple myeloma
Launch Year/Probability:		2020/75%
2024 Sales	Morningstar	$700 million (includes bb21217)
	Consensus	$883 million
Market Model:		multiple myeloma (p.188)

BCMA-targeting CAR-T cell therapy bb2121 entered development in February 2016 and had stellar data at ASCO 2017, with an overall response rate of 100% (and a 27% complete response rate) in nine patients with a median of seven lines of prior therapies. The cell therapy entered the pivotal Karmma study in late 2017 and this study showed an overall response rate of 73% including 33% of patients showing a complete response, which is impressive given the median of six prior therapies (ASCO 2020).

This is a very competitive field, as Nanjing Legend Biotech's CAR-T therapy LCAR-B38M/JNJ-4528 has had strong data (albeit in a study in China in patients with a median of five prior therapies), and partner J&J is in phase 1/2 with the drug in the U.S and the drug showed 100% overall response rate and 86% complete response rate (ASCO 2020).

Celgene and Bluebird Bio also moved into Karmma-2 (high-risk second-line patients) and Karmma-3 (third-line patients) in 2018 and plan to move into a phase 2 study in first-line patients.

This drug is one of three drugs connected to the CVR that would need to get approval by March 31, 2021. The drug was filed with the FDA on March 31, 2020 but rejected by the FDA due to concerns around the CMC (chemistry, manufacturing and control) issues. However, Bristol expects to refile the drug by the end of July. While the drug has breakthrough status, the drug doesn't have priority review status (which includes a 6-month review timeline). Nevertheless, given the critical nature of the disease, we would expect a faster review. In Europe, the drug was accepted for review in May 2020.

Product:		next-gen Revlimid (Iberdomide and CC-92480)
Composition:		small molecules (immunomodulator/IMiD)
Economics:		—
Therapeutic Area:		multiple myeloma
Launch Year/Probability:		2024/30%
2022 Sales:	Morningstar	Not meaningful, in other sales
	Consensus	no estimate
Market Model:		multiple myeloma (p. 188)

CC-92480 and iberdomide are potential next generation drugs with similar mechanisms of actions as Revlimid.In phase 1, iberdomide got 30% of highly refractive multiple myeloma patients to achieve a response. CC-92480 similarly showed strong data in early stage studies in highly refractive patients with multiple myeloma.

Product:		CC-93269
Composition:		Biologic (targets BCMA and CD3 on T-cells)
Economics:		—
Therapeutic Area:		multiple myeloma
Launch Year/Probability:		2024/30%
2022 Sales:	Morningstar	Not meaningful, in other sales
	Consensus	no estimate
Market Model:		multiple myeloma (p. 188)

CC-93269 is a T-cell engager with limited early stage data. However, in a heavily pretreated multiple myeloma patient group (median of 5 prior lines of therapy), the drug helped achieve a complete response in 44% of patients.

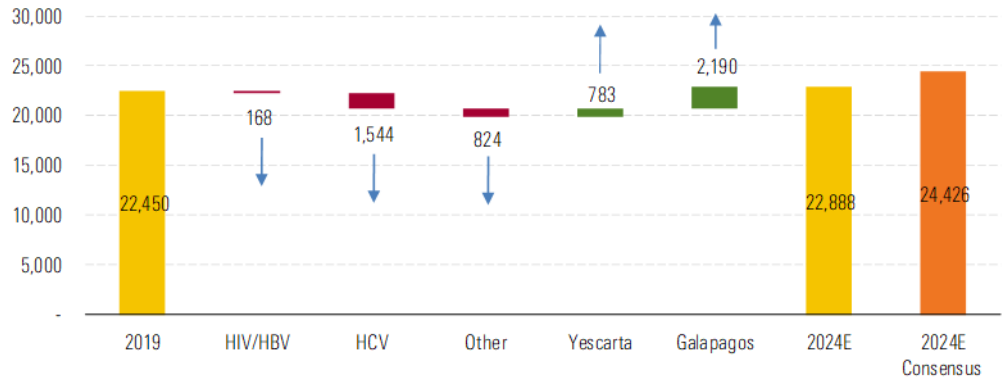
Product:		Cendakimab
Composition:		Biologic (IL-13)
Economics:		—
Therapeutic Area:		Eosinophilic Esophagitis
Launch Year/Probability:		2024/30%
2022 Sales:	Morningstar	Not meaningful, in other sales
	Consensus	no estimate
Market Model:		

Phase 2 data showed very strong data versus placebo. While limited treatment options are available now, this is a therapeutic area that could get crowded with several drugs targeting IL areas likely to gain approval over the next couple years. Also, with only 700,000 people globally (according to Bristol) with this disease, the market might be too small to offer significant opportunity.

Gilead GILD

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$85.00	0.90	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst, Visible Alpha for consensus.

As Hepatitis C Pressure Lessens, HIV Growth Flattens; Pipeline Looks Galapagos-Dependent

Expiring Patents

Viread, Truvada, and Atripla saw generic competition beginning in 2017 in Europe. In the U.S. (80% of Gilead's global HIV sales), Viread saw generic competition in 2018, and Truvada and Atripla will follow in Q4 2020. However, strong launches of newer HIV products defend Gilead's top line.

Inline Products

Gilead's TAF-based HIV regimens, led by Genvoya and Biktarvy, are rapidly taking share from older TDF-based regimens. In addition, HCV sales are poised to shrink to only $2 billion by 2021, decreasing the impact for continuing pricing pressure on Gilead's top line (this business is dwarfed by the $18 billion HIV and hepatitis B portfolio). CAR-T therapy Yescarta is launching slowly, and we've lowered our peak sales estimate to $1.3 billion from $2 billion as effective but more convenient competition launches.

Pipeline

In NASH, Gilead's selonsertib failure likely pushes potential sales to 2024 (novel combination with Novo Nordisk's semaglutide to generate phase 2 data in H2 2020), so most pipeline potential over the next five years ties to the Galapagos collaboration in immunology. This is led by filgotinib, which is poised to see global approvals in rheumatoid arthritis in H2 2020 and could see sales in ulcerative colitis beginning in 2021. We also expect phase 2 data for GLPG-1972 in H2 2020 in osteoarthritis and phase 3 data for GLPG-1690 in IPF in 2021. We expect COVID-19 antiviral remdesivir to see $3 billion peak sales in 2021, but don't model sales extending to 2024. In oncology, magrolimab MDS data is due in 2021.

Moat and Product Portfolio

Expiring Patents

Product:		Truvada
Composition:		small molecule (2 NRTIs)
Economics:		—
Therapeutic Area:		HIV, treatment and prophylaxis
Patents/Generic Threats:		2020 U.S./2017 EU
2024 Sales:	Morningstar	—
	Consensus	$100 million
Market Model:		HIV (p.190)

Truvada's sales began to shrink in the second half of 2016 as the launch of Gilead's next-generation drug Descovy began to ramp in the U.S. and Europe. Truvada still sees strong use in the prophylaxis setting, which now accounts for the majority of demand in the U.S. However, multiple single-tablet regimens are lowering Truvada's use as a treatment for HIV, and Descovy is rapidly replacing Truvada in both indications in 2020. While Teva gained U.S. approval of its generic Truvada in 2017, a settlement pushed the launch to Sept 30, 2020. European patents expired in July 2017.

Product:		Atripla
Composition:		small molecule (2 NRTIs and 1 NNRTI)
Economics:		pay Sustiva portion of sales to Bristol
Therapeutic Area:		HIV
Patents/Generic Threats:		2020 U.S./2017 EU
2024 Sales:	Morningstar	$25 million
	Consensus	$50 million
Market Model:		HIV (p.190)

Atripla sales began to decline as Gilead's other single-tablet regimens Complera and Stribild launched, and declines have accelerated with the launch of the new TAF-based regimens and generic versions of Gilead's older TDF-based regimens in Europe. A Teva settlement allows a generic Atripla launch on Sept 30, 2020.

Inline Products

Product:		Harvoni (Sovaldi+ GS-5885/ledipasvir)
Composition:		small molecule (one nucleotide analog and one NS5A inhibitor)
Economics:		—
Therapeutic Area:		hepatitis C, genotype 1
Patents/Generic Threats:		2030 U.S./EU
2024 Sales:	Morningstar	$150 million ($1.4 billion GILD HCV sales)
	Consensus	$1.6 billion GILD HCV sales
Market Model:		HCV (p.192)

Gilead's rapid develop of Pharmasset's nucleotide inhibitor Sovaldi gave it the first all-oral regimen in hepatitis C, and unprecedented efficacy, safety, and convenience made this Gilead's most valuable molecule. Combination pill Harvoni reached the market in the third quarter of 2014 and was met with sky-high demand, as it allows a shorter eight-week treatment duration for some patients and the removal of interferon in the lucrative genotype 1 niche. As the patient pool shifts toward earlier-stage (healthier) patients, more are eligible for cheaper, shorter regimens, and payers have negotiated prices down aggressively. Harvoni remains Gilead's first-line HCV treatment option for genotype 1 but has faced strong competition since late 2017 from AbbVie's eight-week regimen, Mavyret. Mavyret's list price of only roughly $26,000 per cure dramatically pulled down U.S. net pricing close to $20,000 a year in 2018, and Mavyret also gained patient share via PBM formulary changes.

Product:		Genvoya (TAF-based "Stribild")
Composition:		small molecule (2 NRTIs, integrase inhibitor, and booster)
Economics:		—
Therapeutic Area:		HIV
Patents/Generic Threats:		2029 U.S./2028 EU
2024 Sales:	Morningstar	$1.7 billion
	Consensus	$2.4 billion
Market Model:		HIV (p.190)

A TAF-based version of Stribild, Genvoya launched impressively in 2016, and TAF's renal and bone density benefits over tenofovir (Viread) should allow Gilead to retain HIV sales despite patent expirations on tenofovir-based single-tablet regimens like Atripla, Complera, and Stribild. However, we expect Gilead to heavily promote the bictegravir-based regimen Biktarvy (approved in 2018) over Genvoya, as it does not require a booster (boosters can cause drug-drug interactions, which are increasingly relevant for the aging HIV population). Therefore, Genvoya growth slowed in 2018 and turned negative in 2019. Genvoya should see some global sales stability, however, as it was added to China's National Reimbursement Drug List in January 2020.

Product:		Epclusa (sofosbuvir+velpatasvir/GS-5816)
Composition:		small molecule (1 nucleotide analog and 1 NS5Ainhibitor)
Economics:		—
Therapeutic Area:		hepatitis C, genotypes 1-6
Patents/Generic Threats:		2032 U.S./EU
2024 Sales:	Morningstar	$1.2 billion ($1.4 billion GILD HCV sales)
	Consensus	$1.2 billion ($1.6 billion GILD HCV sales)
Market Model:		HCV (p.192)

This combination pill containing sofosbuvir and pan-genotypic NS5A GS5816 was approved in 2016. Epclusa shortens treatment duration for genotype 3 patients to 12 weeks and effectively replaces Sovaldi in patients with genotypes 2 and 3. We expect Epclusa to remain Gilead's first-line option for these genotypes, but have seen significant pricing pressure and market share erosion since 2018 from AbbVie's Mavyret (an eight-week, pangenotypic regimen). Epclusa was approved in China in May 2018 and added to the National Reimbursement Drug List in January 2020, and the product's standard 12-week regimen makes it a solid option in this market (as patients do not need to be genotyped). However, a difficult IP situation (Gilead's sofosbuvir patent expires in 2024, and key claims have already been withdrawn due to litigation), lack of initial coverage on the national reimbursement list, and competition make this a relatively small opportunity in our model, despite 10 million HCV patients affected in the country.

Product:		Odefsey (TAF-based "Complera")
Composition:		small molecule (2 NRTIs and 1 NNRTI)
Economics:		pay Edurant portion to J&J
Therapeutic Area:		HIV
Patents/Generic Threats:		2025 U.S./2026 EU
2024 Sales:	Morningstar	$1 billion
	Consensus	$1.3 billion
Market Model:		HIV (p.190)

This TAF-based version of Complera launched in 2016, and renal and bone density benefits over tenofovir (Viread) should allow Gilead to retain HIV sales despite patent expirations on tenofovir-based single-tablet regimens like Atripla, Complera, and Stribild.

Product:		Descovy (TAF-based "Truvada")
Composition:		small molecule (2 NRTIs)
Economics:		—
Therapeutic Area:		HIV
Patents/Generic Threats:		2022 U.S. (2025 likely) 2026 EU
2024 Sales:	Morningstar	$2.6 billion
	Consensus	$2.8 billion
Market Model:		HIV (p.190)

This TAF-based version of Truvada launched in 2016, and renal and bone density benefits over tenofovir (Viread) should allow Gilead to retain HIV sales despite Truvada's patent expiration. We expect Descovy patents to be extended to 2025-26. Discover, Gilead's 5,000+ patient prophylaxis trial, proved Descovy non-inferior to Truvada; the most recent 96-week update continued to show a trend toward an efficacy benefit (although insignificant) and significant bone and renal safety advantages (slight BMD declines with Truvada but gains with Descovy, as well as worse eGFR and renal biomarkers with Truvada). While there is some debate on the clinical significance of this benefit, Descovy received prophylaxis approval in the U.S. in October 2019, allowing more Truvada sales to transition to Descovy. Gilead expects 40-45% of U.S. PrEP use from Descovy by the time Truvada generics launch in Q4 2020, and as of the end of Q1 2020, Gilead had 241,000 patients in the U.S. on PrEP, roughly 22% of the 1.1 million individuals who could benefit from HIV prophylaxis, and 38% were taking Descovy (versus Truvada). Positive data for Glaxo's bimonthly injection cabotegravir in the prophylaxis setting (66% more effective at preventing infection than Truvada, albeit likely due to Truvada noncompliance) and a potential all-gender label (Descovy's label is limited to men and transgender women) could weigh on Gilead's long-term Descovy growth, although we already assume generic pressure by 2025.

Product:		Complera/Eviplera
Composition:		small molecule (2 NRTIs and 1 NNRTI)
Economics:		pay Edurant portion to J&J (GILD retains up to 30% of J&J share)
Therapeutic Area:		HIV
Patents/Generic Threats:		2025 U.S./2026 EU
2024 Sales:	Morningstar	$75 million
	Consensus	$75 million
Market Model:		HIV (p.190)

Complera's safety profile initially drew patients away from Atripla and gave Gilead more favorable profit-sharing terms. However, Complera began to decline rapidly in late 2016 as Gilead launched its newer TAF-based regimen, Odefsey.

Product:		Stribild
Composition:		small molecule (2 NRTIs, integrase inhibitor, and booster)
Economics:		—
Therapeutic Area:		HIV
Patents/Generic Threats:		2029 U.S./2028 EU
2024 Sales:	Morningstar	—
	Consensus	$100 million
Market Model:		HIV (p.190)

Stribild is a single-tablet regimen that incorporates Gilead's integrase inhibitor elvitegravir, boosting agent cobicistat, and the two nucleotide analogs in Truvada, giving Gilead access to all the economics of the drug. Stribild initially gained market share as a treatment option for naive patients and switches from older integrase-based regimens that included Merck's Isentress. However, Stribild is being replaced by Gilead's newer TAF-based regimens (including Genvoya and Biktarvy), and sales began to decline in late 2016.

Product:		Vemlidy (TAF)
Composition:		small molecule (NRTI)
Economics:		—
Therapeutic Area:		HBV
Patents/Generic Threats:		2022 U.S. (2025 likely)/2026 EU
2024 Sales:	Morningstar	$1.5 billion
	Consensus	$600 million
Market Model:		—

Gilead gained FDA approval for Vemlidy in hepatitis B in 2016, where its safety profile should allow it to replace Viread's position in the field. Gilead sees a more than $1 billion HBV franchise by 2022 based on U.S., but particularly China growth potential. Vemlidy was approved in China in November 2018. Roughly 20 million people in China meet guidelines for treatment, accounting for a third of patients globally, and 300,000 die in China each year due to HBV-related liver cirrhosis. Vemlidy was added to China's National Reimbursement Drug List in January 2020.

Product:		Vosevi (sofosbuvir + velpatasvir + voxilaprevir)
Composition:		small molecule (nucleotide analog, NS5A, and protease inhibitor)
Economics:		—
Therapeutic Area:		hepatitis C, genotypes 1-6
Patents/Generic Threats		2034 U.S./EU 2033
2024 Sales:	Morningstar	$50 million ($1.4 billion GILD HCV sales)
	Consensus	$1.6 billion GILD HCV sales
Market Model:		HCV (p.192)

Gilead's pan-genotypic triplet regimen entered the HCV market in 2017, which adds protease inhibitor voxilaprevir to its two-drug Epclusa regimen. The drug is approved in the U.S. as a 12-week regimen, as Polaris-2 and Polaris-3 studies failed to show noninferiority of eight-week Vosevi to 12-week Epclusa. This limited the potential of this therapy to serve as the central HCV treatment in Gilead's portfolio and also makes Gilead more vulnerable to AbbVie's Mavyret (approved in 2017 as an eight-week regimen in noncirrhotics). However, in Europe, Vosevi was approved as an eight-week regimen for noncirrhotic patients on par with Mavyret. We expect Vosevi is most likely to serve as a salvage regimen for patients who failed prior treatments that include an NS5A inhibitor.

Product:		Yescarta/KTE-X19 (axi-cel)
Composition:		cell therapy (CAR-T) targeting CD19
Economics:		—
Therapeutic Area:		DLBCL (2L and 3L)
Patents/Generic Threats		2027 U.S./EU manuf. patents pending (EU comp of matter expired)
2024 Sales:	Morningstar	$1.2 billion
	Consensus	$1.2 billion
Market Model:		NHL (p.185)

Acquired as part of the $11.9 billion Kite deal in 2017, Yescarta launched in third-line DLBCL in the U.S. in late 2017 and in Europe in late 2018. Initial uptake has been slowed by training at transplant centers and Medicare reimbursement challenges, but we think durable efficacy in patients with complete responses secure a place for CAR-T therapy in relapsed DLBCL. We forecast a Yescarta sales plateau reaching $1.2 billion by 2024, driven largely by uptake in 20% of patients with second-line or later DLBCL. The ZUMA-7 study (data H2 2020 and filing 2021) pits Yescarta against transplant in the second-line setting, and we expect CAR-T therapy to expand to this setting, but not first-line therapy (phase 2 data expected in 2021, but this is already served well with Rituxan-based regimens). Smaller indications like ALL (2021E approval) and mantle cell lymphoma (Aug 2020E approval for KTE-X19, which is similar to Yescarta but has a slightly different manufacturing process) offer minor upside. Gilead also hopes to gain approval in indolent forms of NHL, and data at ASCO 2020 showed an 80% complete response and 68% ongoing response at nine months among third-line patients (grade 3 or higher CRS and neurological events were 8% and 17%); we expect data on primary analysis at 12 months in late 2020 and approval in 2021, although responses do not yet look as durable as in DLBCL. Combination with checkpoint inhibitors appears less likely, as a combination with Tecentriq in Zuma-6 did not yield better efficacy than Yescarta alone (AACR 2020), but Gilead plans to explore combination with CD47 antibody magrolimab. While Novartis' Kymriah was approved in pediatric/young adult ALL in August 2017 and launched at a price of $475,000 (a one-time treatment), Gilead priced Yescarta at $373,000, likely due to the drug's larger targeted patient population. We expect net pricing is slightly lower and will decline with time as value-based contracts are signed and as new competition enters the market. Among CAR-T therapies in DLBCL, Yescarta has the most data on durability of response and a strong manufacturing record. Novartis received approval for Kymriah in DLBCL in May 2018 (to file in 2021 for 2L DLBCL and follicular lymphoma), although DLBCL-specific manufacturing issues have given Gilead a dominant position on this market. Celgene's CAR-T therapy liso-cel, with a potentially differentiated safety profile, and Incyte/Morphosys' off-the-shelf CD19 targeting antibody tafasitamab could launch in mid-2020 (August 2020 PDUFAs In the long run, off-the shelf CAR-T therapy, like Allogene's ALLO-501 (positive phase 1 data at ASCO 2020), could compete, although Gilead's KITE-037 is in preclinical development.

Product:		Biktarvy (B/F/TAF)
Composition:		small molecule (2 NRTIs and integrase)
Economics:		—
Therapeutic Area:		HIV
Patents/Generic Threats		U.S./EU 2033
2024 Sales:	Morningstar	$9.1 billion
	Consensus	$10 billion
Market Model:		HIV (p.190)

Biktarvy received FDA approval in February 2018 and EU approval in June 2018, and the rapid launch in the U.S. has gone even faster than Genvoya, with roughly 20% of Biktarvy patients switching from Glaxo regimens. Gilead tested Biktarvy (a TAF-based regimen with nonboosted integrase inhibitor bictegravir) against Glaxo's combo pill Triumeq and other regimens that include Glaxo's integrase inhibitor, Tivicay, and data in 2017 showed noninferiority; overall, it confirmed the renal and bone density benefits and broader safety benefits of TAF over Glaxo's Epzicom backbone (in Triumeq), but appeared to point to Tivicay as a slightly more potent integrase. Biktarvy is allowing Gilead to slowly regain lost market share from Glaxo and steal share from small HIV players (doctors preferred nonboosted regimens, as they involve fewer drugs and side effects and a lower risk of drug/drug interactions, and Genvoya has a booster). However, we assume mild price headwinds could emerge as Glaxo seeks to expand usage of its two-drug regimens. Biktarvy was also approved in China in Aug 2019; better screening is leading to growing diagnoses in this market (150,000 diagnosed in 2018), and the government has provided free treatment since 2003.

Product:		Veklury/remdesivir
Composition:		small molecule (nucleotide analog)
Economics:		—
Therapeutic Area:		SARS-CoV-2 (COVID-19)
Patents/Generic Threats:		U.S. 2034 (2014 first filing)
2024 Sales:	Morningstar	$3 billion peak (2021)
	Consensus	$1.7 billion peak (2021)
Market Model:		—

Overall, we think remdesivir has place in the near to mid-term as a treatment for patients who are hospitalized with COVID-19 but not yet on mechanical ventilation, although we expect vaccines and other treatments to reduce demand significantly beyond the next couple of years. Remdesivir received emergency use authorization in the U.S. on May 1 as a treatment for severely ill, hospitalized patients with COVID-19, and was approved as Veklury in Japan in May and in Europe in July 2020. The drug has broad antiviral activity across RNA viruses including SARS, MERS, and now SARS-CoV-2. It is a nucleotide analog inhibitor of RNA-dependent RNA polymerases first tested in Ebola, where efficacy didn't stack up to Regeneron's REGN-EB3. However, with the New England Journal of Medicine report in late January indicating that one patient responded to treatment for a novel coronavirus, Gilead rapidly moved into late-stage testing in both mild/moderate and severely ill patients. Data supporting the EUA came April 29 from the NIH study Actt-1, where remdesivir improved recovery time by 31% and had a trend toward improved mortality rates versus placebo (8% versus 11.6%). On May 22, published details from the Actt-1 study pointed to the highest benefit among patients receiving oxygen therapy, but not yet on mechanical ventilation. Data from the Simple study in severely ill patients showed that 5 and 10-day dosing of remdesivir led to similar outcomes for patients, which extends Gilead's drug supply to more patients. We estimate that roughly 1.7 million patients could receive commercial drug in the second half at the 5-day dosing schedule, using Gilead's estimate of total supply for 1 million patients by the end of 2020 at the 10-day dosing schedule. Based on Gilead's expected run rate by the fourth quarter of 2020, we think there could be enough remdesivir to treat an additional 6 million patients in 2021. NIH and Simple study data were part of the roller coaster of remdesivir-related news, following the April 23 leaked draft of disappointing data from a controlled but incomplete study in severe patients in China (now published in the Lancet, which showed that the study was weakened by lower enrollment and the long delay between patient diagnosis and treatment), the April 17 leak of positive University of Chicago experiences with the now-disclosed Simple study, and the April 10 publication of encouraging (but uncontrolled) data from U.S. compassionate use patients. Data from Gilead's controlled study in moderate patients, released June 1, showed a statistically significant 65% higher likelihood of improvement for five-day dosing of remdesivir over standard of care in hospitalized patients with pneumonia, but not on oxygen therapy, although other measures of improvement were not statistically significant. Initial supply is being donated, but we expect commercial sales to begin in the second half of 2020, and we assume average pricing near the disclosed developed market price of $2,340 for government payers. This price is in line with the price deemed justified by cost effectiveness watchdog ICER, which estimated in a June 24 analysis an updated price benchmark of $2,520-$2,800 per patient, assuming remdesivir is compared with dexamethasone (a potential new standard of care based on recent data) and that remdesivir is able to prove a survival benefit (recent data point to a trend toward a survival benefit but have not yet proven statistically significant).We assume a 40% probability of sales for government stockpiling at a lower price (around $1,000 per course), which could mimic Tamiflu stockpiling if recurrence fears rise. However, we also only model sales through 2023, as we assume stockpiles will be sufficient to cover a significant share of the population by then, and there should also be effective vaccines on the market by this time. Gilead started a phase 1 trial of inhaled remdesivir in healthy volunteers in July 2020, with the aim of testing this method of administration in COVID-19 patients in August. An inhaled version could allow Gilead to treat non-hospitalized patients, potentially preventing hospitalization in some patients (the current infused version would be difficult to extend into healthier patients).

Moat Trend and Product Pipeline

Product:		filgotinib
Composition:		small molecule (JAK1 inhibitor)
Economics:		Galapagos has 50/50 co-promote option in Europe, global royalties >20%
Therapeutic Area:		Crohn's disease, RA, ulcerative colitis
Launch Year/Probability:		2020/80%
2024 Sales:	Morningstar	$1.6 billion
	Consensus	$1 billion
Market Model:		RA (p.167), Crohn's/UC (p.168)

Filgotinib is most advanced in RA, where Gilead filed for approval in multiple geographies in 2019 (the Dec 2019 U.S. filing was paired with a priority review voucher, so a mid-2020 approval is likely, with a H2 2020 launch in all major geographies). Overall, we think filgotinib has a leading safety profile among JAKs (although it may not avoid the class black box warning for thrombosis), and we think similar efficacy to other JAKS in RA and slightly lower efficacy in ulcerative colitis should still be sufficient to generate $3 billion in peak sales. While there is concern of potential for classwide risk of thromboembolic events, we think filgotinib stands out with a differentiated profile among JAKs; pooled safety data from FINCH 1-3 presented at ACR 2019 and from 7 studies as of EULAR 2020 do not show any signal of cardiovascular issues higher than placebo rates. A preclinical signal on testicular safety also does not appear to be a significant issue for filgotinib; interim data from the MANTA study was enough to allow filing in the U.S. (although final data from the study could be delayed beyond 2021, as trial enrollment was paused due to the pandemic), The drug first generated positive phase 3 data from FINCH 2 in 2018 in biologic experienced patients that looks competitive with other JAKs on efficacy (32% ACR70 looks better at the high dose than AbbVie's Rinvoq at 22% in Select-Beyond at the approved 15 mg dose). Data from FINCH 1 (MTX-inadequate responders) and FINCH 3 (MTX naive) in Q1 2019 also supported strong efficacy and safety, although filgotinib was not able to prove superiority to Humira in ACR (Rinvoq, on the other hand, achieved superiority to Humira in the Select-Compare study). Filgotinib is also in phase 3 in Crohn's disease (to complete enrollment in 2021), however, phase 3 data in ulcerative colitis in May 2020 was disappointing, with a roughly 11% placebo-adjusted remission rate after 10 weeks at the 200 mg dose in the Selection study that paled in comparison to the 20% remission rate seen in Rinvoq's phase 2 b study, U-Achieve, in 2018 (at the highest 45 mg dose after eight weeks--remission was 14% at 15 mg dose). We expect filgotinib will be competitive with Pfizer's Xeljanz (approved in RA and UC), AbbVie's Rinvoq (RA approval in 2019, UC and Crohn's approval likely in 2022), and Eli Lilly/Incyte's Olumiant (approved in Europe for RA in 2017 and in the U.S. in 2018). Gilead also generated positive phase 2 filgotinib data in ankylosing spondylitis and psoriatic arthritis in 2018 and began phase 3 PsA Penguin studies in late 2019, but Rinvoq has a lead in these indications. Patents extend to 2030.

Product:		Lenacapavir/GS-6207
Composition:		small molecule (capsid inhibitor)
Economics:		—
Therapeutic Area:		HIV
Launch Year/Probability:		2021/40%
2024 Sales:	Morningstar	$100 million
	Consensus	—
Market Model:		—

This novel Gilead drug could prevent resistance by targeting the capsid shell around HIV RNA, and dosing could be as infrequent as every six months (subcu injection). Phase 1b data in March 2020 showed that a single subcu dose led to significant HIV RNA reductions by day 10 versus placebo, and data in July 2020 showed that this effect was sustained for at least six months. The drug entered a larger phase 2/3 study in late 2019 in heavily treated HIV patients in combination with foundation regimens, and this trial should be enough for a regulatory filing in 2021. A phase 2 trial in treatment-naïve patients also began in late 2019 in combination with oral drugs, with data expected in 2021. Gilead expects to begin a phase 1 trial in PrEP in H2 2020 with a once-weekly oral version of lenacapavir. Lenacapavir could also be combined with recently licensed neutralizing antibodies 3BNC117 and 10-1074, or with a long-acting version of integrase inhibitor bictegravir (which is entering phase 1 in H2 2020).

Product:		Ziritaxestat/GLPG-1690
Composition:		small molecule (autotaxin inhibitor)
Economics:		Gilead has ex-EU rights, pays 20-24% royalty to Galapagos
Therapeutic Area:		IPF
Launch Year/Probability:		2022/50%
2024 Sales:	Morningstar	$300 million
	Consensus	$400 million
Market Model:		—

The most advanced drug in the Galapagos collaboration behind filgotinib, GLPG-1690 is in phase 3 trial Isabela for idiopathic pulmonary fibrosis. Gilead expects a futility analysis in H1 2021. Data from the phase 2a Flora study in 2017 was encouraging, as the drug stabilized forced vital capacity over 12 weeks in 17 patients (8 mL increase), versus a decline (87 mL decrease) in 6 patients in the placebo arm. Approved treatments like Boehringer Ingelheim's Ofev and Roche's Esbriet showed a roughly 30 mL decrease over this time period, emphasizing the need for more effective treatments. Roche saw Esbriet sales of roughly $1.1 billion in 2019. If ziritaxestat succeeds, it could eventually compete with Roche's PRM-151, which was acquired with Promedior in early 2020 and slowed decline in lung function in combination with approved treatments in a phase 2 study. Patents for GLPG-1690 in IPF extend to 2034 in the U.S. and Europe.

Product:		GLPG-1972
Composition:		small molecule (ADAMTS-5 inhibitor)
Economics:		Option on U.S. rights after phase 2b (from Galapagos--Servier holds ex U.S. rights)
Therapeutic Area:		osteoarthritis
Launch Year/Probability:		2023/40%
2024 Sales:	Morningstar	$200 million
	Consensus	$150 million
Market Model:		—

GLPG-1972 is on track to produce data from the phase 2b Roccella study in the second half of 2020 in patients with knee osteoarthritis, after completing enrollment in June 2019. The trial assesses three different doses in more than 850 patients over one year versus placebo. In animal models, the drug effectively targeted a cartilage degrading enzyme, ADAMTS-5, and phase 1 biomarker data in healthy volunteers and osteoarthritis patients also pointed to the drug's potential efficacy.

Product:		magrolimab
Composition:		antibody (CD47)
Economics:		—
Therapeutic Area:		MDS, AML, lymphoma, solid tumors
Launch Year/Probability:		2023/60%
2024 Sales:	Morningstar	$300 million
	Consensus	$300 million
Market Model:		—

Gilead acquired immuno-oncology firm Forty Seven for $95.50 per share or $4.9 billion in cash (deal closed April 2020), in keeping with its strategy to strengthen its oncology pipeline beyond cell therapy with bolt-on acquisitions. Lead Forty-Seven drug magrolimab could be a first-in-class CD47 antibody, with promising early data in hematology indications like MDS and AML (35,000 diagnosed annually in the US combined) and ongoing studies in lymphoma and solid tumors. Its safety profile could allow it to be used in combination with other Gilead drugs like Yescarta or its oral PD-L1 inhibitor, which is still in early testing. In a phase 1b trial in first-line AML and MDS with azacitadine, presented at ASCO 2020, MDS patients saw a 42% complete response rate, and AML patients a 56% CR (this trial now has an MDS arm that could see data in 2021 and lead to approval in late 2022). The Forty Seven acquisition also brings cKIT-targeting FSI-174 and SIRPa-targeting FSI-189, both in preclinical testing, but we are not adding these to our Gilead valuation model until then advance in clinical studies. Magrolimab could eventually compete with many other CD47-targeting drugs like Trillium's phase 1 drug TTI-621 (although it has some thrombocytopenia side effects, next-generation TTI-622 is now in development and could have a better safety profile), ALX Oncology's phase 1 drug ALX148 (being studied in solid tumors with Keytruda), and I-Mab's phase 1 drug TJC4 (aiming for differentiated safety, lower anemia rates). Takeda's NAE inhibitor pevonedistat has also generated encouraging phase 2 efficacy and safety data in high-risk MDS and AML in combination with azacitadine (52% CR in high-risk MDS versus 27% with aza alone), and fully enrolled the phase 3 Panther study in fall 2019.

Product:		GLPG-1205
Composition:		small molecule (GPR84 antagonist)
Economics:		Option for ex-EU rights after phase 2 (from Galapagos)
Therapeutic Area:		IPF
Launch Year/Probability:		2024/30%
2024 Sales:	Morningstar	$100 million
	Consensus	—
Market Model:		—

GPR84 antagonist GLPF-1205 is currently in the phase 2 Pinta trial, which completed recruitment in early 2020 and should produce topline data in H2 2020. The trial will measure the difference in forced vital capacity changes in patients on the drug versus placebo. Mouse data point to the potential of the drug to slow lung damage in IPF patients, and phase 1 data in healthy volunteers showed solid safety data.

Product:		Cilofexor/GS-9674
Composition:		small molecule (FXR agonist)
Economics:		—
Therapeutic Area:		NASH, PBC/PSC
Launch Year/Probability:		2024/30%
2024 Sales:	Morningstar	$100 million (total NASH)
	Consensus	—
Market Model:		—

One of two drugs in Gilead's NASH pipeline, following the failure of selonsertib in phase 3. We model a nearly $18 billion probability-adjusted NASH market in 2029, with a combination involving FXR agonist cilofexor and and ACC inhibitor firsocostat accounting for roughly $1 billion of this. While Intercept's FXR agonist obeticholic acid leads the way (PDUFA June 2020), Gilead believes that cilofexor's structure (not a bile acid mimetic) could mean less cross reactivity and fewer side effects. OCA trials have seen cholesterol elevations and itching, and the drug had a black box warning attached to its label in February 2018 due to recent cases of severe liver damage in niche liver indication PBC. While cilofexor data in NASH at AASLD 2019 indicate less itching than obeticholic acid, cilofexor did not appear particularly effective and failed to see a fibrosis benefit (OCA generated a significant fibrosis benefit). Cilofexor data in combination with firsocostat in Dec 2019 from the ATLAS study was mixed; although Gilead did not meet its primary endpoint (at least 1 stage improvement in fibrosis score without worsening of NASH), there was a trend toward a benefit with the combo over placebo (20.9% versus 10.5%). Itching was also an issue, with 28% of patients seeing mild to moderate itching on the combination (15% on placebo). We think potential efficacy could receive a boost from the in-progress combination with Novo Nordisk's diabetes therapy semaglutide (data expected in the second half of 2020). Cilofexor patents extend to 2032 in the U.S. and Europe.

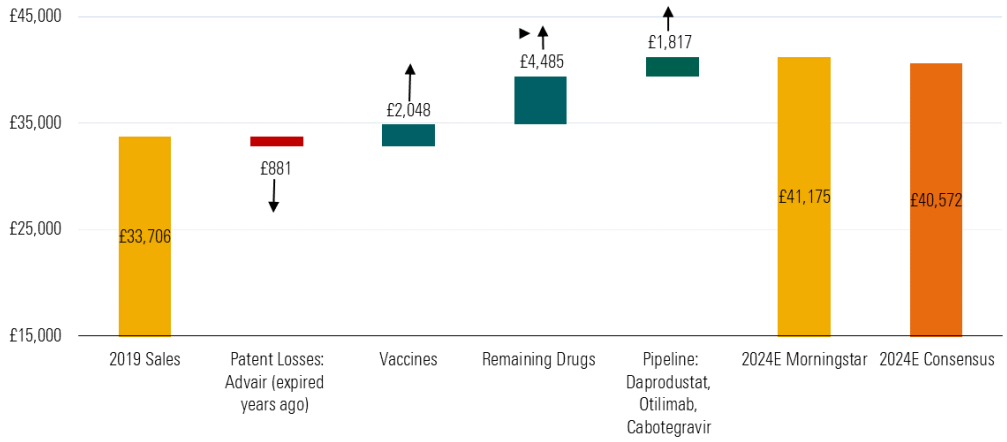
Product:		Firsocostat/GS-0976
Composition:		small molecule (ACC inhibitor)
Economics:		—
Therapeutic Area:		NASH
Launch Year/Probability:		2024/30%
2024 Sales:	Morningstar	$100 million (total NASH)
	Consensus	—
Market Model:		—

One of two drugs in Gilead's NASH pipeline, following the failure of selonsertib in phase 3. We model a nearly $18 billion probability-adjusted NASH market in 2029, with a combination involving FXR agonist cilofexor and and ACC inhibitor firsocostat accounting for roughly $1 billion of this. Gilead's ACC inhibitor has a novel mechanism and generated proof-of-concept data at EASL 2017. AASLD 2017 data showed higher 20 mg daily dose led to significant reduction in buildup of fat in the liver versus placebo at 12 weeks, with hepatic steatosis down by 29% versus 8% for placebo. Also, fibrosis, as measured by TIMP-1, fell 7.9% versus 1.5% for placebo. Proof-of-concept data in combination with selonsertib or FXR agonist cilofexor showed promising impact on liver fat and fibrosis markers, despite short trial duration. Cilofexor data in combination with firsocostat in Dec 2019 from the ATLAS study was mixed; although Gilead did not meet its primary endpoint (at least 1 stage improvement in fibrosis score without worsening of NASH), there was a trend toward a benefit with the combo over placebo (20.9% versus 10.5%). Itching was also an issue, with 28% of patients seeing mild to moderate itching on the combination (15% on placebo). We think potential efficacy could receive a boost from the in-progress combination with Novo Nordisk's diabetes therapy semaglutide (data expected in the second half of 2020).

GlaxoSmithKline GSK

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$45.00	0.91	Medium	Wide	Stable

Revenue Breakdown GBP Millions



Source: Morningstar, company reports, and DrugAnalyst/S&P Cap IQ for consensus.

Advair Competition Remains a Concern, but Diversified Operations Should Drive Growth

Expiring Patents

Generic Advair launched in 2019 and will continue to weigh on sales with an amplified impact on earnings, given the high margin of the drug. The generic competition could also hurt other respiratory drugs because payers are likely to push back and only approve payment for differentiated drugs.

Inline Products

The convenience of Breo (once-daily dosing) is not likely to support pricing power, but solid efficacy (Anoro and Trelegy in chronic obstructive pulmonary disease) should support some pricing power in the face of generic Advair. While pricing power should hold up well in the protected class of HIV, the increasing competitive threat from Gilead is likely to decelerate growth in this class for Glaxo. Outside of the drug group, the strong entrenchment in vaccines (some cost advantages) should offset the pressures in the respiratory division. In particular, shingles vaccine Shingrix is well positioned to generate peak sales above GBP 6 billion when additional manufacturing comes online in 2024.

Pipeline

While Glaxo's pipeline still looks weak, it is improving. The heavy focus on next-generation respiratory drugs moved the firm away from therapeutic areas with strong pricing power. However, the firm's recent move back into cancer should help growth prospects with its BCMA drug.

Moat and Product Portfolio

Expiring Patents

Product:		Seretide/Advair
Composition:		small molecule (ICS/LABA)
Economics:		—
Therapeutic Area:		asthma/COPD
Patents/Generic Threats:		Diskus 2016 U.S./expired international; HFA device 2018-26 U.S./2017 international
2024 Sales	Morningstar	GBP 849 million
	Consensus	GBP 889 million
Market Model:		nonbiologic respiratory (p.170)

While branded pressures have caused pricing to fall over the past several years, the sales declines accelerated in 2019 with the introduction of the first generic drugs in the U.S.

Inline Products

Product:		Shingrix
Composition:		vaccine
Economics:		—
Therapeutic Area:		Zoster vaccine (shingles)
Patents/Generic Threats:		2026
2024 Sales	Morningstar	GBP 3,254 million
	Consensus	GBP 3,342 million
Market Model:		—

Despite Merck's vaccine selling around $1 billion (with only 30% penetration in the U.S.), we believe Glaxo's vaccine will achieve significantly higher sales due to the stronger efficacy over Merck and the relatively low global penetration of Merck's vaccine. The key phase 3 study completed in 2014 and showed 97% efficacy, much better than Merck's efficacy of 50%. However, the two-dose requirement is more cumbersome than Merck's one dose. (Glaxo's vaccine still achieves 90% efficacy at one dose, but it is hard to determine if this response is persistent.) The vaccine was approved in October 2017 in the U.S. followed by the Centers for Disease Control's advisory committee recommendation to use the vaccine over Merck's vaccine for people 50 and older (versus the previous recommendation of 60 and older). However, Glaxo has been supply-constrained with Shingrix and vaccine sales should be stable at around GBP 2.1B annually through 2024 when an additional plant comes on line.

Product:		Anoro
Composition:		small molecule (LAMA/ LABA)
Economics:		6.5% to 10% to Theravance
Therapeutic Area:		COPD
Patents/Generic Threats:		2025 U.S./2029 Europe
2024 Sales	Morningstar	GBP 783 million
	Consensus	GBP 705 million
Market Model:		nonbiologic respiratory (p.170)

Given the once-daily dosing and superiority to Spiriva, Anoro should have solid long-term prospects in COPD. Anoro is one of the few drugs to show superiority over another drug in the same class. However, the strength of the drug may show the most as a component of the triple drug Trelegy.

Product:		Breo/Relvar	While once-daily dosing is better than Advair (twice daily) and insurance coverage is improving, we expect Breo to gain only close to a third of Advair's market share in asthma and COPD as there is no clear efficacy benefit over Advair. Also, we expect sales declines in the U.S. for Breo in the near term due to poor pricing dynamics as generic Advair is fairly equivalent to Breo.
Composition:		small molecule (ICS/LABA)	
Economics:		15% on first $3 billion of sales and 5% thereafter to Theravance	
Therapeutic Area:		asthma/COPD	
Patents/Generic Threats:		2022 U.S./2027 Europe	
2024 Sales	Morningstar	GBP 1,165 million	
	Consensus	GBP 994 million	
Market Model:		nonbiologic respiratory (p.170)	

Product:		Trelegy	Trelegy has shown solid data (outperformed Astra's high-dose Symbicort in Fulfil and outperformed Breo and Anoro in Impact). While Chiesi's triple COPD drug Trimbow is already launched in Europe, Trelegy has the first-mover advantage in the U.S. Astra's competitive triple should reach the market in 2021. Phase 3 data in asthma reported in mid-2019 looked encouraging but missed the secondary endpoint of reducing exacerbation, so the insurance coverage in asthma might be more difficult. The drug was filed with the FDA in late Oct. 2019 and with EMEA in Feb. 2020 for asthma.
Composition:		small molecule (ICS/LABA/LAMA)	
Economics:		15% on first $3 billion of sales and 5% thereafter to Innoviva	
Therapeutic Area:		COPD	
Patents/Generic Threats:		2027 U.S./2029 Europe	
2024 Sales	Morningstar	GBP 1,890 million	
	Consensus	GBP 1,738 million	
Market Model:		nonbiologic respiratory (p.170)	

Product:		Juluca (dolutegravir + Edurant)	Based on an agreement with J&J in June 2014, Glaxo is combining Tivicay with J&J's Edurant (old-guard NNRTI) in the maintenance setting (patients already achieving viral suppression on a three-drug regimen). In the phase 3 Sword studies, Glaxo's doublet showed 95% continued viral suppression at 48 weeks (noninferior to 3- and 4-drug combo regimens) in already virologically suppressed patients. However, the drug was largely studied in patient populations where virus suppression has already been achieved, limiting the sales potential of the drug.
Composition:		small molecules (integrase + NNRTI)	
Economics:		high teens to Shionogi (hits cash flows, not core EPS), equity positions in ViiV Healthcare are GSK: 78%, Pfizer: 12%, and Shionogi:10%	
Therapeutic Area:		HIV (maintenance)	
Patents/Generic Threats:		2027 U.S./2029 Europe	
2024 Sales	Morningstar	GBP 962 million	
	Consensus	GBP 758 million	
Market Model:		HIV (p.190)	

Product:		Tivicay	Tivicay (once daily) holds potentially best-in-class status, supported by the Sailing study that outperformed twice-daily integrase inhibitor Isentress. Key head-to-head data from Gilead with its new integrase inhibitor bictegravir (with no booster) showed the drugs to be noninferior. However, given Gilead's strong combination drugs and entrenchment in the HIV market, we expect Tivicay to decline slightly in the near term.
Composition:		small molecule (integrase inhibitor)	
Economics:		high teens to Shionogi (hits cash flows, not core EPS), equity positions in ViiV Healthcare are GSK: 79%, Pfizer: 12%, and Shionogi: 10%	
Therapeutic Area:		HIV	
Patents/Generic Threats:		2027 U.S./2029 International	
2024 Sales	Morningstar	GBP 1,694 million	
	Consensus	GBP 1,388 million	
Market Model:		HIV (p.190)	

Product:		Triumeq
Composition:		small molecule (integrase inhibitor/NRTI)
Economics:		high teens to Shionogi (hits cash flows, not core EPS), equity positions in ViiV Healthcare are GSK: 79%, Pfizer: 12%, and Shionogi: 10%
Therapeutic Area:		HIV
Patents/Generic Threats:		2027 U.S./2031 international
2024 Sales	Morningstar	GBP 2,207 million
	Consensus	GBP 1,868 million
Market Model:		HIV (p.190)

Adding abacavir and lamivudine (both NRTIs) to Tivicay, this all-in-one combination offers convenience and efficacy, but the abacavir component has shown an elevated risk of myocardial infarction. Sales of this drug will likely come under continued pressure from both Gilead's Biktarvy and Glaxo's Dovato.

Product:		Nucala
Composition:		biologic (IL-5)
Economics:		—
Therapeutic Area:		asthma
Patents/Generic Threats:		2027 U.S./2025 Europe (data exclusivity)
2024 Sales	Morningstar	GBP 1,107 million
	Consensus	GBP 1,171 million
Market Model:		biologic respiratory (p.171)

The IL-5 space is crowded with Astra's Fasenra approved in November 2017 and Teva's Cinqair approval in early 2016. Glaxo's first-mover advantage and strong entrenchment in the respiratory area should lead to strong market share. Also, Cinqair will likely only have IV administration (failed in subcu studies in early 2018) compared with Nucala's subcutaneous convenience. However, Astra's Fasenra gained approval for eight-week dosing, better than Nucala's four-week dosing. In the smaller refractory setting (3%-5% of 300 million asthma patients worldwide) and at a price of $30,000 annually, the drug is well positioned. Further, an indirect comparison versus Fasenra and Cinqair showed better results for Nucala. Also, Nucala showed positive phase 3 data in nasal polyps in April 2020 (first IL-5 to show this data). However, in COPD, one phase 3 study was successful (Metrex low dose) while another failed (Metreo high dose), which led to the FDA rejection in late 2018.

Product:		Zejula
Composition:		small molecule (PARP)
Economics:		gained drug through $5 billion acquisition of Tesaro: Royalty in teens to Merck; partnered with J&J in prostate
Therapeutic Area:		cancer (ovarian first)
Patents/Generic Threats:		2030
2024 Sales	Morningstar	GBP 866 million
	Consensus	GBP 916 million
Market Model:		

While Zejula looks similar in efficacy to the other PARPs, the drug's development timeline looks behind Astra/Merck's Lynparza, which has approvals in first- and second-line ovarian cancer, prostate cancer, breast cancer and strong first-line maintenance ovarian cancer data in Solo-1 (PFS HR of 0.30). Zejula was initially approved for second-line maintenance ovarian cancer (5,000 patients drug treated in the U.S.), but the FDA approved the drug for first line ovarian cancer (regardless of biomarker status) in April 2020 based on the data from Prima in first-line maintenance ovarian cancer which looked good, but slightly worse than Lynparza, except in the HRD negative group (potentially over 35% of ovarian cancer population), where the drug looks better than Lynparza. The progression free survival hazard ratios for Zeljua were 0.40, 0.50 and 0.68 in the BRCA (20% of patients), HRD+ (30%) and HRD- (50%) groups, which compares to Lynparza ratios of 0.31, 0.43, and 0.92. (The lower the hazard ratio, the better.) One side effect concern for Zejula is thrombocytopenia (bleeding problem), but this is reversable. With 84,000 patients on treatment in the top eight countries in this indication, the drug holds potential. Several more ovarian cancer studies should read over the next two years. Also, a small cell lung cancer study in Chinese patients should complete in 2020.

Product:		Dovato (Dolutegravir + lamivudine)
Composition:		small molecules (integrase + NRTI)
Economics:		high teens to Shionogi (hits cash flows, not core EPS), equity positions in ViiV Healthcare are GSK: 78%, Pfizer: 12%, and Shionogi:10%
Therapeutic Area:		HIV
Patents/Generic Threats:		2027 U.S./2029 Europe (pediatric approval could expand these dates)
2024 Sales	Morningstar	GBP 1,351 million

Dovato gained approval in most markets in 2019 (Japan Jan. 2020). This two-drug combo gets rid of cardiovascular concerns with abacavir (a component in Triumeq). Despite Tivicay's strong resistance profile, questions remain as to whether this regimen is strong enough to control the disease, as standard of care today includes three-drug regimens. In naive patients (Gemini 1 and 2), the doublet versus dolutegravir plus Truvada showed noninferiority at 48 weeks, without risking treatment resistance, which was largely confirmed with two-year data in 2019. We expect that steady long-term efficacy could begin to improve physician confidence in a two-drug regimen. Additionally, data from Tango

	Consensus	GBP 952 million
Market Model:		HIV (p.190)

(reported in July 2019) showed non-inferiority versus TAF containing treatment (a standard treatment) in virally suppressed patients that switched treatment.

Moat Trend and Product Pipeline

Product:		Rukobia/fostemsavir/BMS-663068
Composition:		small molecule (attachment inhibitor)
Economics:		ViiV structure and 13% to 25% to Bristol
Therapeutic Area:		HIV
Launch Year/Probability:		2020/100%
2024 Sales	Morningstar	GBP 144 million
	Consensus	GBP 218 million
Market Model:		HIV (p.190)

In early 2014, a phase 2 study (254 patients) showed the drug had similar efficacy as Reyataz boosted with ritonavir and a better side effect profile. 69%-80% of fostemsavir patients had HIV-1 RNA levels of less than 50 c/mL compared with 75% of patients taking Reyataz with ritonavir. Also, the new mechanism of action could be important for patients not responding to current therapies. In the phase 3 study Brighte (heavily pretreated patients failing therapy), 54% of patients achieved virologic suppression (less than 40 c/mL). Glaxo filed the drug in late 2019 (U.S.) and early 2020 (Europe) following data collection related to manufacturing site changes. The FDA approved the drug in June 2020. We expect this drug to be reserved for highly refractory patients, but high pricing could support stronger sales.

Product:		Cabotegravir
Composition:		small molecule (integrase)
Economics:		high teens to Shionogi (hits cash flows, not core EPS), equity positions in ViiV Healthcare are GSK: 78%, Pfizer: 12%, and Shionogi:10%
Therapeutic Area:		HIV
Launch Year/Probability:		2020/75%
2024 Sales	Morningstar	GBP 625 million
	Consensus	GBP 620 million
Market Model:		HIV (p.190)

Cabotegravir is a long-acting HIV integrase inhibitor that could be administered once monthly or once every two months. The phase 3 Flair and Atlas studies evaluate four-week dosing for the drug in combination with Edurant (rilpivirine), and both studies reported positive data in early 2019 with the exception of patients with the subtype strain of HIV1a (typically found in Russia, Eastern Europe and Africa). Also, the ATLAS-2M looking at eight-week dosing reported positive data in August 2019, opening up a longer duration of treatment option. This intramuscular injection could be painful and may limit uptake of the drug, but we expect eight-week dosing could be an appealing option for some patients and adherence rates were high in clinical development. The drug was filed in the U.S. (April 2019) and Europe (July 2019), but received a complete response letter from the FDA regarding manufacturing concerns in December 2019. Canada was the first company to approve the drug in March 2020. Additionally, data in the prophylaxis setting ($2 billion annual market in the U.S. and only 20% penetrated) is looking strong as well with the first Phase III study (HPTN083) showing 66% more efficacy than Truvada. A second prophylaxis study (HPTN084) should report in late 2020 and includes cisgender women (Descovy prophylaxis doesn't include women in the label).

Product:		Belantamab mafodotin/GSK2857916
Composition:		Biologic (anti-CD38 antibody-drug conjugate)
Economics:		Minor payments to Seattle Genetics and royalty payments to Biowa
Therapeutic Area:		multiple myeloma
Launch Year/Probability:		2020/75%
2024 Sales	Morningstar	GBP 299 million
	Consensus	GBP 754 million
Market Model:		multiple myeloma (p.188)

The drug has received breakthrough designation from the FDA and early-stage data looks encouraging, but not up to the level of BCMA-targeted CAR-T therapies. However, the drug's off-the-shelf profile could be appealing to patients, even with a slightly reduced efficacy profile. In an early-stage study of 35 patients, the drug showed an overall response rate of 60% in refractory patients (50% had 5 or more treatments). In a larger study (Dreamm-2, 132 multiple myeloma patients), the overall response rate was 31% following 7 previous lines of therapy. The company filed the drug in Jan. 2020 (U.S.) and Feb. 2020 (Europe) on the Dreamm 2 data. While approved therapies Pomalyst, Kyprolis, Darzalex have shown overall response rates of 24-31%, the patients had only 5 lines of previous treatment. Also, CAR-T BCMA therapies have seen ORRs north of 80% (88% for J&J's JNJ-68284528 and 94% for Celgene/Bluebird's bb2121). One concerning side effect is keratopathy (eye problems), but the severity rate was largely low. There are 36,000 patients in the G7 with third- or fourth-line disease, and Glaxo could expand into the third-line setting in 2022 with Dreamm-3 data. Dreamm-7 and 8 (second line) should read out in 2023, supporting an approval in this setting in 2023-24 (50,000 patients in G7). First-line studies are just starting but could eventually support expansion here as well (56,000 patients in G7).

Product:		Daprodustat
Composition:		small molecule HIF-PHI
Economics:		Partnered with Kyowa in Japan
Therapeutic Area:		chronic kidney disease
Launch Year/Probability:		2020 (Japan)-2022(Global)/40%
2024 Sales	Morningstar	GBP 220 million
	Consensus	GBP 223 million
Market Model:		—

Daprodustat has completed several smaller phase 2 studies and two phase 3 studies (Ascend-D, switching from ESA and Ascend-ND, switching from ESA or naive to ESA) should complete in late 2020. A smaller Japanese phase 3 study reported in late 2018, showing noninferiority to Aranesp for hemodialysis dependent patients, supporting a Japanese filling in Aug. 2019. However, we are concerned that Astra's roxadustat will establish a strong entrenchment before daprodustat.

Product:		Dostarlimab
Composition:		biologic (PD-1)
Economics:		Gained from Tesaro acquisition
Therapeutic Area:		cancer
Launch Year/Probability:		2020/90%
2024 Sales	Morningstar	GBP 103 million
	Consensus	GBP 334 million
Market Model:		—

While the drug is late to the PD-1/PDL1 landscape, approval looks likely in MSI high endometrial cancer based on strong data from the Garnet study with an overall response rate of 49% in the MSI high group. Ovarian (data in 2021) and confirmatory endometrial studies (data in 2021) are the next key events for the drug. The drug was filed in late 2019.

Product:		Gepotidacin
Composition:		small molecule (TT inhibitor)
Economics:		Partnership with U.S. government
Therapeutic Area:		antibiotic
Launch Year/Probability:		2022/75%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	$76 million
Market Model:		—

While most companies have moved away from antibiotic drug development, Glaxo is continuing. Gepotidacin is a novel antibiotic (triazaacenaphthylene topoisomerase inhibitor). Phase 2 data in gonorrhea and bacterial skin infections were strong with 95% efficacy for the bacterial elimination of gonorrhea with one dose. The phase 3 studies Eagle 1 (gonorrhea) and Eagle 2 (urinary tract infection) should report in 2021. However, with pricing so challenging and doctors wanting to limit new antibiotic use, we don't expect robust sales.

Product:		GSK33596609
Composition:		biologic (ICOS agonist)
Economics:		Royalties to INSERM
Therapeutic Area:		cancer
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	GBP 25 million
	Consensus	GBP 136 million
Market Model:		—

This novel oncology drug candidate has shown good early stage data (regardless of PDL1 expression) in head and neck cancer (ESMO 2019) and a registrational study should complete in the same patient group in 2023 in combination with Keytruda. Several other earlier stage studies are ongoing.

Product:		M7824
Composition:		biologic (TGF-Beta Trap and PDL-1)
Economics:		EUR 300M upfront to Merck KGaA and up to EUR 3.7B in total milestones
Therapeutic Area:		cancer
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	Not meaningful by 2024
	Consensus	GBP 543 million
Market Model:		—

The drug is a bifunctional immunotherapy that targets TGF-Beta and PD-L1. The dual mechanism should broaden the response seen with just PD-L1 targeted therapies. A phase 2 (potentially pivotal) study in refractory non-small cell lung cancer (head to head versus Keytruda) should report in late 2021. Another phase 2 (head to head versus Imfinzi) in stage 3 lung cancer should report in 2024. Also, a phase 2/3 study in biliary cancer (liver related) should report in 2022. Overall, while early stage data look encouraging, the phase 2 and 3 studies are needed to gain better insights on the effectiveness of the drug.

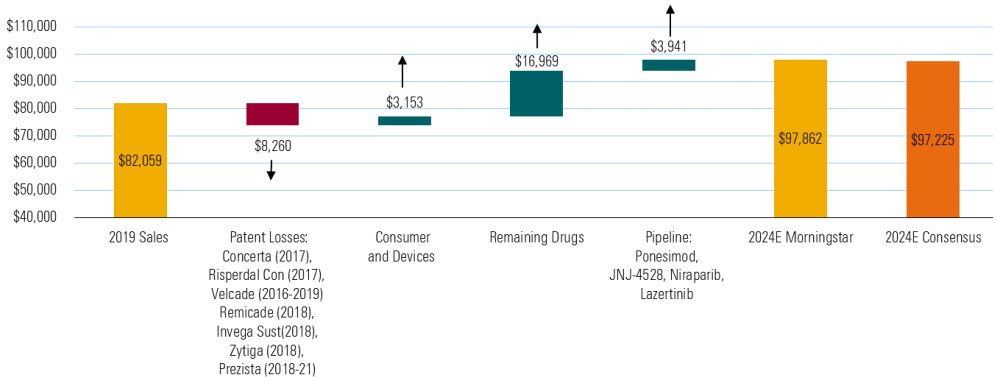
Product:		Otilimab GM-CSF
Composition:		biologic (GM-CSF)
Economics:		Double digit royalties to Morphosys
Therapeutic Area:		Rheumatoid Arthritis
Launch Year/Probability:		2023/60%
2024 Sales	Morningstar	GBP 150 million
	Consensus	GBP 116 million
Market Model:		RA (p. 167)

Otilimab is an antibody targeting cytokine granulocyte macrophage colony-stimulating factor (GM-CSF). Glaxo decided to take the drug into phase 3 development following mixed phase 2 data (Baroque) where the drug didn't hit its primary endpoint but trended well at 16% versus 3% for placebo as defined by DAS28. Also, the data doesn't look as good as data generated by JAK inhibitors. The phase 3 studies include head to head comparisons to Pfizer's Xeljanz and Kevzara and should begin to report in late 2021.

Johnson & Johnson JNJ

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$141.00	1.01	Low	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst/S&P Cap IQ for consensus.

Solid Recently Launched Drugs Help Offset Major Patent Pressures and a Weak Pipeline

Expiring Patents

Johnson & Johnson has several drugs facing generics, but due to the complexity of the drug or the patent estate, the exact timing is uncertain. We model generic competition for Concerta (2017), Risperdal Consta (2017), Velcade (2016-19), Remicade (2017), Invega Sustenna (2018), Zytiga (2018), and Prezista (2018) over the next five years. However, the majority of these drugs will face slower declines due to their complexity. In particular, Remicade's biologic structure and J&J's defensive bundling strategies are limiting biosimilar pressures.

Inline Products

For core product without near term patent losses, we expect steady growth due to new indications and excellent data for cardiovascular drug Xarelto, cancer drugs for Darzalex and Erleada, and immunology data for Tremfya.

Pipeline

Johnson & Johnson has reinvigorated its mid to late-stage pipeline with a strong focus in oncology. While several of the late stage drugs have only limited early stage data, we believe this accelerated development of drugs in areas of unmet medical need with strong pricing power will help the company offset its long-term patent losses.

Moat and Product Portfolio

Expiring Patents

Product:		Remicade
Composition:		biologic (anti-TNF)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		2017 U.S./2015 international
2024 Sales	Morningstar	$1,605 million
	Consensus	$1,675 million
Market Model:		RA (p.167), UC/Crohn's (p.168), psoriasis (p.166)

With two biosimilars already on the market in the U.S. from powerhouses Pfizer and Merck, we expect Remicade to post annual declines of over 15% over the next five years. However, the complexity of the hospital administration and J&J's protective discounting has blocked success and biosimilars haven't gained any meaningful share to date. The biosimilar challenges are shown by Pfizer's recent legal claims against J&J alleging exclusionary contracts that provide rebates for using Remicade. We expect increased discounting by biosimilars (beyond the current 30%+ discount) will eventually break Remicade's position.

Product:		Prezista
Composition:		small molecule (protease inhibitor)
Economics:		—
Therapeutic Area:		antiretroviral (HIV)
Patents/Generic Threats:		2017 U.S./2018 International (2020+)
2024 Sales	Morningstar	$682 million
	Consensus	$1,785 million
Market Model:		HIV (p.190)

The high barrier to resistance for Prezista has made it a popular component of HIV combination regimens, but the rise of the integrase class is likely to limit further uptake. That said, J&J's new combination pill Symtuza (which also includes Gilead's NRTIs TAF and emtricitabine and booster cobicistat) was approved in the U.S. in July 2018 and could help further entrench the drug. Agreements with generic companies will likely delay generic Prezista competition in the U.S. until 2021.

Product:		Zytiga
Composition:		small molecule (antiandrogen)
Economics:		license with BTG
Therapeutic Area:		prostate cancer
Patents/Generic Threats:		2016 U.S./2022 international
2024 Sales	Morningstar	$1,069 million
	Consensus	$647 million
Market Model:		—

Data exclusivity should keep generic competition at bay until 2022 in Europe. However, branded competition from Pfizer's Xtandi will likely intensify with Xtandi's lack of need for steroids and 17-month benefit before chemo is needed (versus eight-month for Zytiga). Also, the strong data from the Latitude study in high-risk metastatic hormone-naive prostate cancer (38% reduction in death) will help drive sales, as well, but largely in Europe where the drug still has exclusivity protection.

Product:		Invega Sustenna/Trinza
Composition:		small molecule (dopamine antagonist)
Economics:		license with Alkermes
Therapeutic Area:		schizophrenia
Patents/Generic Threats:		2013-18 U.S./2017 international
2024 Sales	Morningstar	$3,146 million
	Consensus	$4,710 million
Market Model:		—

Generic pressure should cause sales of Invega Sustenna (monthly dosing) to decline, but manufacturing complexity and Invega Trinza (quarterly dosing) could offer some protection against generic Sustenna. Also, the company is pursuing 6-month dosing that could extend patent protection around the franchise longer.

Product:		Stelara
Composition:		biologic (IL 12/23)
Economics:		—
Therapeutic Area:		psoriasis, Crohn's
Patents/Generic Threats:		Early 2024 U.S.(assumes pediatric extension)/Jan. 2024 Europe
2024 Sales	Morningstar	$9,774 million
	Consensus	$9,448 million
Market Model:		psoriasis (p.166), Crohn's/UC (p.168)

While the drug will likely lose market share in psoriasis (50% of current sales) to the higher-efficacy IL17s and IL 23s, the drug's strong efficacy in Crohn's (35% of current sales) should offset these losses leading to stable long-term sales. The rest of sales (rheumatoid arthritis and psoriatic arthritis) should be more stable. A head-to-head study versus Humira in Crohn's should report out in mid-2020. Also, the drug gained approval in ulcerative colitis in late 2019, opening up almost 30% more patients.

Inline Products

Product:		Simponi
Composition:		biologic (anti-TNF)
Economics:		—
Therapeutic Area:		RA
Patents/Generic Threats:		2024 U.S./international
2024 Sales	Morningstar	$2,355 million
	Consensus	$2,456 million
Market Model:		RA (p.167)

With a monthly subcu dosing advantage as well as the option for IV dosing, this TNF should retain market share when biosimilars launch against Remicade and Humira, but aggressive payers could push back. More recent indications in ankylosing spondylitis and psoriatic arthritis in 2017 should also help preserve share.

Product:		Imbruvica
Composition:		small molecule (BTK)
Economics:		50% profits to AbbVie
Therapeutic Area:		hematology
Patents/Generic Threats:		Nov. 2027 U.S. (assumes Hatch Waxman Patent Term Extension) Oct. 2026-29 Europe
2024 Sales	Morningstar	$5,065 million
	Consensus	$6,374 million
Market Model:		CLL (p.187), MM (p.188), NHL (p.185)

Imbruvica is approved for several indications, including mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, relapsed/refractory marginal zone lymphoma, and refractory chronic graft-versus-host disease (cGVHD). We believe that with an 84% reduction of death as compared with chlorambucil in first-line CLL, Imbruvica is well positioned to take share in CLL. AbbVie expects non-risk-adjusted sales of $11 billion by 2025, which seems high, especially after the drug's failure in Phoenix (non-GCB DLBCL).

However, more share gains in first-line CLL are possible, given the positive data (OS HR of 0.17) from E1912 at ASH 2018 in younger/more fit patients taking Imbruvica plus Rituxan versus chemo plus Rituxan, which was added to the U.S. label in April 2020. Also, positive data from Illuminate (1L CLL less fit) with Gazyva versus chemo plus Gazyva should help in first-line CLL. Share of first-line CLL is 50% in the U.S. (30% starting as first line), so there is room to grow, but total patient share in second-line CLL is close to 75% under treatment, suggesting some saturation. Key upcoming studies include Selene in RR FL (2020), but early-stage data in FL looked poor. Also, the drug did fail in Resolve (pancreatic cancer).

The biggest competitive threat in CLL is from Astra's BTK Calquence, which posted progression free survival (PFS) improvements of 69% (refractory mono versus Rituxan plus idelalisib or Rituxan plus bendamustine) and 90% (first line combined with Gazyva versus Gazyva plus chlorambucil). Imbruvica posted PFS improvements of 78% (refractory versus Arzerra) and 77% (first line combined with Gazyva versus Gazyva plus chlorambucil). Safety looks slightly better with Calquence, which had serious adverse rates of 39% versus 58% for Imbruvica in the first-line setting with atrial fibrillation a key outlier (3% versus 12% for Imbruvica), but headache and bleeding rates were better for Imbruvica. A head to head study versus Calquence should report out in March 2021 in the refractory CLL patient group.

One other threat is from Beigene's Brukinsa (already approved for mantle cell lymphoma), which should have a head to head Phase 3 study versus Imbruvica report out in early 2021 in refractory CLL.

Product:		Xarelto
Composition:		small molecule (anticoagulant)
Economics:		royalty to Bayer for U.S. sales, up to 30% of sales
Therapeutic Area:		deep vein thrombosis
Patents/Generic Threats:		2027 U.S.
2024 Sales	Morningstar	$3,458 million
	Consensus	$2,503 million
Market Model:		atrial fibrillation (p.172)

Xarelto's once-daily dosing/first mover advantage in AF, DVT/PE, and ACS (EU)—a $20 billion-plus market—should net 30% share (up from 25% currently) versus PFE/BMY's Eliquis netting 50%+ (up from 45% currently, twice daily dosing, but with mortality benefit) and warfarin (20% market share currently). The positive data in PCI (Pioneer versus warfarin) and coronary artery disease (CAD) and peripheral artery disease (PAD) (Compass versus aspirin) should add $3 billion and $10 billion in market potential, respectively. The Compass data showed a 24% MACE reduction, good compared with statins (20%-30%), GLP-1 (low to mid-20s), SGLT-2s (midteens), and PCSK-9s (15%). However, educating physicians to use an anticoagulant in CAD/PAD has proved challenging and uptake has been slow. Important label expansion opportunities should produce data over the next few years, including PAD (Voyager, $2 billion opportunity, 2020) and several smaller patient population studies.

Product:		Invokana
Composition:		small molecule (SGLT2)
Economics:		license from Mitsubishi Tanabe
Therapeutic Area:		diabetes
Patents/Generic Threats:		2027 U.S./2024 EU
2024 Sales	Morningstar	$617 million
	Consensus	$441 million
Market Model:		noninsulin diabetes (p.175)

Despite the first-mover advantage in the U.S. in the SGLT2 class, the drug's side effects of ketoacidosis, amputations, and acute kidney injury along with strong efficacy and safety data from competitor Jardiance will likely mean flat sales for the drug. In particular, the black-box warning for amputation risk will likely limit growth for the drug. However, positive renal outcomes data (for patients with type 2 diabetes and chronic kidney disease) was added to the label in Oct. 2019, which should help stabilize the drug's usage as close to a third of type 2 diabetics have kidney disease.

Product:		Darzalex
Composition:		biologic (CD38)
Economics:		midteens royalty to Genmab
Therapeutic Area:		multiple myeloma
Patents/Generic Threats:		2031 U.S./EU
2024 Sales	Morningstar	$7,433 million
	Consensus	$7,325 million
Market Model:		multiple myeloma (p.188)

First approved as monotherapy in 4L+ MM, Darzalex rapidly expanded into 2L MM with Pollux (combo with Revlimid) and Castor (combo with Velcade) studies, and then into first line with study Alcyone (with Velcade). Phase 3 MM study Maia (combining Darzalex with Revlimid with a PFS HR of 0.55) and Cassiopeia (combining Darzalex with Velcade and thalidomide, complete response of 29% versus 20%) reported positive data and were included in the label in 2019. Also, an easier to take subcutaneous version of the drug was approved by the FDA and in Europe in the second quarter of 2020.

Product:		Tremfya/guselkumab
Composition:		biologic (IL-23)
Economics:		license from Morphosys
Therapeutic Area:		psoriasis
Patents/Generic Threats:		Aug. 2027 U.S. (with potential extensions to 2031)/Dec. 2031 EU
2024 Sales	Morningstar	$2,853 million
	Consensus	$2,963 million
Market Model:		psoriasis (p.166) crohn's/UC (p. 168)

Tremfya was approved in 2017 in moderate to severe psoriasis based on positive data from Voyage 1 (750 moderate to severe psoriasis patients: PASI 90 of 85% versus 66% for Humira at 16 weeks), Voyage 2 (1,000 moderate to severe psoriasis patients: PASI 90 of 71% versus 51% for Humira), and Navigate (800 moderate to severe psoriasis patients failing to respond to Stelara: IGA score showing 0 or 1 and 2 or more grades of improvement for 31% of patients compared to 14% for Stelara). J&J's head-to-head study versus Novartis' IL-17 Cosentyx (Eclipse) showed superior PASI 90/100 data at 48 weeks, but the data was not better at 12 weeks, which supports Cosentyx's faster onset of action. Also, a competitive head-to-head study versus Taltz (funded by Eli Lilly) in psoriasis showed superiority over Tremfya at a 12-week endpoint for PASI 100 of 41% versus 25% for Tremfya, but we expect the drugs are more similar as the duration of treatment continues, as IL-23s tend to take longer to work. Phase 3 studies in psoriatic arthritis (Discover 1 and 2, reported in late 2019) showed effective response rates similar to TNFs and IL-17s, and J&J filed for approval in this indication in September 2019 (U.S.) and Europe (October 2019). Crohn's (including a Stelara comparator) and ulcerative colitis studies should report in mid-2022.

Product:		Opsumit	Opsumit is an endothelin receptor antagonist that has unique mortality data that should help shield the drug from Tracleer's generic pressures. Potential expansion into the CTEPH (5-10% of PAH patients) could help drive sales, but the FDA complete response letter in 2019 may mean more clinical work is needed.
Composition:		small molecule (ERA)	
Economics:		Royalties to Nippon Shinyaku	
Therapeutic Area:		pulmonary arterial hypertension	
Patents/Generic Threats:		2025 U.S./2026 EU	
2024 Sales	Morningstar	$1,923 million	
	Consensus	$1,930 million	
Market Model:		—	

Product:		Uptravi	The drug looks better positioned that United's Orenitram, and earlier use with Opsumit positions it well for growth. Tritan data in 2020 could expand use into triple combination with Opsumit and Adcirca.
Composition:		small molecule (prostacyclin)	
Economics:		Royalties to Nippon Shinyaku	
Therapeutic Area:		pulmonary arterial hypertension	
Patents/Generic Threats:		Apr. 2023 (U.S. with patent restoration potentially out to 2026), Apr. 2027 OUS	
2024 Sales	Morningstar	$1,405 million	
	Consensus	$1,577 million	
Market Model:		—	

Product:		Erleada/ARN-509	J&J gained the drug through a $650 million acquisition of Aragon Pharmaceuticals in mid-2013. The drug's efficacy (0.28 HR in reduction in metastasis-free survival versus 0.29 for Xtandi) looks very similar to Pfizer's Xtandi. However, a new competitor from Bayer showed good overall survival data with Nebeqa (OS HR of 0.69 versus 0.78 for Erleada) setting up more competition. In early 2018, Erleada was approved in the U.S. nonmetastatic CRPC based on the Spartan study (70,000 patients in the G7). The label was expanded in late 2019 to include the positive data from the Titan study in hormone-sensitive prostate cancer (Titan) in 2019 (35,000 patients). J&J expects to file in localized nonmetastatic setting (Atlas) in 2021 (600,000 patients), and in chemo-naive metastatic patients (Acis) in 2021 (or later) with Zytiga and prednisone, where Zytiga is already approved (more than 75,000 patients).
Composition:		small molecule (antiandrogen)	
Economics:		acquired from Aragon	
Therapeutic Area:		prostate cancer	
Patents/Generic Threats:		Sept. 2030/ March 2027 Europe	
2024 Sales	Morningstar	$2,734 million	
	Consensus	$1,831 million	
Market Model:		—	

Product:		Spravato/esketamine	The phase 3 data for this drug is mixed. One phase 3 study showed a benefit of the drug in reducing a depression rating scale by 4 and 8 points, respectively, for the 56 mg and 84 mg doses. Another phase 3 study (in elderly patients) missed the primary endpoint, but numerically favored the drug. Other late stage studies showed more supportive data, enough for the drug to gain approval in 2019. At a cost of close to $50,000 and mixed data, we expect the drug will be reserved for only the sickest patients. According to the National Institute of Health, close to 7% of people in the U.S. have had a major depressive episode and current and data from Wiles Thomas in Health Technology Assessment showed that a third of patients didn't respond to after four courses of treatment, opening up a large potential market for Spravato. Also, while there are no composition of matter patents, method of use patents go out to March 2027, providing potentially more protection in the U.S.
Composition:		small molecule (NMDA antagonist)	
Economics:		—	
Therapeutic Area:		depression	
Patents/Generic Threats:		2024 U.S./2029 Europe	
2024 Sales	Morningstar	$623 million	
	Consensus	$1,110 million	
Market Model:		—	

Product:		Balversa/Erdafitinib/JNJ-493
Composition:		small molecule (FGFR 1,2,3,4)-15% of bladder cancer
Economics:		licensed from Astex
Therapeutic Area:		cancer
Patents/Generic Threats:		Apr. 2031/pending in Europe
2024 Sales	Morningstar	$391 million
	Consensus	$463 million
Market Model:		—

In an early phase 1 study (37 patients), the drug showed one close to complete response in urothelial cancer and one partial response in bladder cancer. At ASCO 2018, the drug showed a 40% overall response rate (better than IO drugs) in urothelial (bladder) cancer patients with FGFR mutations. The FDA approved the drug in April 2019 for bladder cancer. Cancers high in FGFR mutations include bladder (20%), glioblastoma (21%), head and neck (9%), non-small cell lung cancer (4%). A phase 3 study in refractory bladder cancer (with FGFR mutations) versus Keytruda should complete in November 2020.

Moat Trend and Product Pipeline

Product:		Pimodivir
Composition:		small molecule (PB2)
Economics:		licensed from Vertex
Therapeutic Area:		influenza
Launch Year/Probability:		2021/30%
2024 Sales	Morningstar	$216 million
	Consensus	NA
Market Model:		—

Pimodivir has shown good phase 2 data in reducing viral loads in patients with the flu. Phase 3 studies in flu should report in 2020 (at risk of getting the flu) and 2020 (infected with the flu). J&J didn't highlight this drug as a drug with potential over $1 billion annually, suggesting some concern by management.

Product:		Ponesimod
Composition:		small molecule (S1P1)
Economics:		
Therapeutic Area:		MS
Launch Year/Probability:		2020-21/80%
2024 Sales	Morningstar	$486 million
	Consensus	$200 million
Market Model:		MS (p.177)

While this drug was not moved quickly into phase 3 development by Actelion, J&J moved ahead with the drug. The phase 3 study Optimum showed ponesimod to be superior to Aubagio at the MS meeting ECTRIMS (Sept. 2019), setting up a filing in the U.S. and Europe in March 2020. Additional phase 3 studies should complete in mid-2022 (long-term safety), 2020 (safety as add on to Tecfidera). J&J didn't highlight this drug as a drug with potential over $1 billion annually, suggesting some concern by management.

Product:		JNJ-4528
Composition:		biologic (BCMA CAR-T)
Economics:		licensed from Legend Biotech with 50/50 profit split, except China where the split is 30/70 (J&J/Legend)
Therapeutic Area:		multiple myeloma
Launch Year/Probability:		2021/75%
2024 Sales	Morningstar	$1.1 billion
	Consensus	NA
Market Model:		multiple myeloma (p.188)

While early in development, J&J is signaling it could file the drug by 2021. J&J started a phase 1/2 study in the U.S. in summer 2018 and hopes its dual-binding site (versus one for Celgene/Bluebird Bio's bb2121) could allow for differentiated efficacy. In the Cartitude phase 1/2 study (presented at ASH 2019 and ASCO 2020), the response rate was an impressive 100% (86% complete response) for multiple myeloma patients who had a median of five prior therapies. Bristol's competing CAR-T therapy ide-cel/bb2121 showed an overall response rate of 81% including 35% of patients showing a complete response in updated data at ASCO 2020, which should be enough to gain approval in late 2020, but doesn't compare as well with J&J's evolving data.

Product:		Cusatuzumab
Composition:		Biologic (CD70)
Economics:		
Therapeutic Area:		Cancer/AML
Launch Year/Probability:		2021
2024 Sales	Morningstar	$306 million
	Consensus	NA
Market Model:		

Cusatuzumab inhibits CD70, potentially leading to the death of leukemia cells. In a phase 1/2 study, the drug showed a complete response rate of 67% in treatment naïve AML patients. A phase 2 study should complete in late 2020.

Product:		Niraparib
Composition:		Small molecule (PARP)
Economics:		Partnered with GSK
Therapeutic Area:		Prostate cancer
Launch Year/Probability:		2023/90%
2024 Sales	Morningstar	$350 million
	Consensus	NA
Market Model:		

Niraparib (Zejula) is a PARP in development for prostate cancer, where J&J holds rights to the drug. Phase 2 data in third line prostate cancer showed complete responses for 62% of the BRCA mutant group and 24% for non-BRCA patients. Phase 3 data in prostate cancer (Magnitude study) should report out in mid-2022. However, we expect Lynparza's first mover advantage (filed with the FDA in prostate cancer in early 2020) will limit gains for niraparib in this indication.

Product:		Lazertinib/JNJ-1937
Composition:		Small molecule (EGFR)
Economics:		
Therapeutic Area:		Cancer EGFR
Launch Year/Probability:		2023/80%
2024 Sales	Morningstar	$396 million
	Consensus	NA
Market Model:		

Lazertinib is a next generation EGFR targeting drug. In a phase 1/2 study, the drug showed a response rate of 69% in EGFR refractory patients. A phase 3 study versus Iressa should report in late 2022. We would be more hopeful for the study if the comparator was the market leading drug Tagrisso rather than Iressa. However, a doublet of lazertinib plus JNJ-6372 could be very powerful.

Product:		JNJ-7564
Composition:		Biologic (bispecific antibody for CD3 and GPRC5D)
Economics:		Partnered with Genmab
Therapeutic Area:		Multiple myeloma
Launch Year/Probability:		2023-24
2024 Sales	Morningstar	$270 million
	Consensus	NA
Market Model:		MM (p. 188)

Very limited data is available for the drug, but the theory of hitting T-cells with CD3 and GPRC5D on multiple myeloma cells looks intriguing.

Product:		Amivantamab/JNJ-6372
Composition:		Biologic (bispecific to EGFR and cMet)
Economics:		Partnered with Ganmab
Therapeutic Area:		EGFR lung cancer
Launch Year/Probability:		2023
2024 Sales	Morningstar	$396 million
	Consensus	NA
Market Model:		

JNJ-6372 showed good early stage data and efficacy in Tagrisso resistant patients. In a phase 1 study, the drug showed an overall response rate of 41% in refractory non-small cell lung cancer with Exon 20 insertion mutations that typically don't respond to chemotherapy or other TKIs. A 400-patient study in non-small cell lung cancer should complete in early 2021

Product:		Aprocitentan
Composition:		Small molecule (endothelin receptor antagonist)
Economics:		20-35% of sales to Idorsia
Therapeutic Area:		Hypertension
Launch Year/Probability:		2023/40%
2024 Sales	Morningstar	$90 million
	Consensus	NA
Market Model:		

Aprocitentan is in phase 3 development (Precision study) for treatment resistant hypertension with data likely in early 2021. Phase 2 data showed a solid dose dependent response with limited side effects.

Product:		AAV-RPGR/CNGB3
Composition:		Gene therapy
Economics:		
Therapeutic Area:		Rare eye diseases
Launch Year/Probability:		2024
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		

While studies are in the early stage, the theory behind the gene therapy holds potential in rare disease eye settings like achromatopsia (10,000 people in the U.S.) and X-linked retinitis (7,500 people in the U.S.).

Product:		JNJ-4500
Composition:		Biologic (NKG2D)
Economics:		
Therapeutic Area:		Crohn's and ulcerative colitis
Launch Year/Probability:		2024
2024 Sales	Morningstar	$150 million
	Consensus	NA
Market Model:		crohn's/UC (p. 168)

With limited data available, the phase 2 Trident study (data in 2021) in Crohn's will be important in determining the potential of the drug. The theory behind the drug is blocking NKG2D could reduce stress and inflammation in intestines, potentially opening up a new treatment mechanism for Crohn's and ulcerative colitis.

Product:		Seltorexant/JNJ-7922
Composition:		Small molecule (orexin-2 antagonist)
Economics:		Partnered with Minerva
Therapeutic Area:		Major depression
Launch Year/Probability:		2024/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		

Seltorexant is in phase 2 development for major depression. Earlier phase 2 data showed the drug was statistically significant in improving depression scores for patients failing traditional SSRIs and SNRIs. The drugs ability to help people sleep might be part of the effectiveness of the drug. The timeline on the drug's development is less clear, but phase 2 studies should complete in 2020, guiding phase 3 development.

Product:		Ad26.RSV.preF
Composition:		Vaccine
Economics:		
Therapeutic Area:		RSV
Launch Year/Probability:		2024/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		

Single immunization with JNJ's RSV vaccine produced durable immune responses. Major phase 2 studies should complete in 2021.

Product:		Teclistamab/JNJ-7957
Composition:		B-cell maturation antigen (BCMA) and CD3
Economics:		
Therapeutic Area:		Multiple myeloma
Launch Year/Probability:		2024/25%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		MM (p. 188)

In a phase 1 study at ASCO 2020, the drug showed efficacy of a 67% response rate at the highest dose in a patient group with a median of 6 prior treatments in relapsed multiple myeloma.

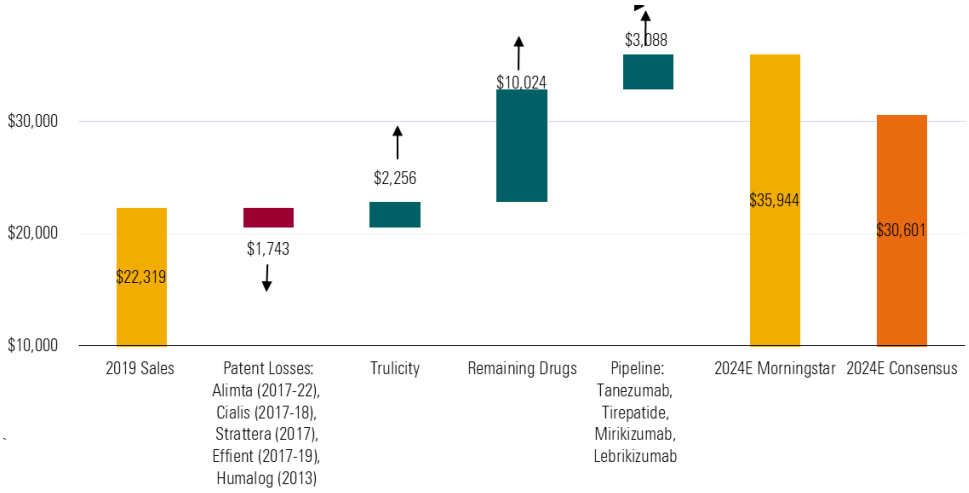
Product:		BMS-986177
Composition:		Small molecule (FXIa inh.)
Economics:		Share profits with Bristol
Therapeutic Area:		
Launch Year/Probability:		2024/40%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		—

BMS-986177 is a small molecule Factor XIa inhibitor in development for stroke and venous thromboembolism prevention. Phase 2 studies should complete in 2021, setting a decision for phase 3 development.

Eli Lilly LLY

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$154.00	1.08	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst/S&P Cap IQ for consensus.

New Drugs Are Well Positioned to Drive Growth, but Patent Losses are Still Weighing on Growth

Expiring Patents

Cialis (2017) and Alimta (2017-22) represent the biggest patent headwinds for Eli Lilly, but it faces relatively modest headwinds over the next five years. Additionally, while a biosimilar has launched against insulin Humalog, the pricing pressure seems limited unless additional entrants emerge.

Inline Products

The diabetes market has lost some pricing power for insulins and oral medicines, which has hurt Eli Lilly, but the strength of the GLP1 market has more than offset this, setting Eli Lilly's Trulicity up for strong growth. Also, Eli Lilly's recent entry into immunology with Taltz and Olumiant should drive strong sales. Additionally, Verzenio's strong data in the adjuvant breast cancer market adds a major growth driver.

Pipeline

Next-generation pain (tanezumab), diabetes (GLP1/GIP1), and immunology (mirikizumab and lebrikizumab) set the company up well. Eli Lilly's ability to replenish its late-stage pipeline despite recent approvals is impressive. While not modeled for significant sales, Eli Lilly also holds midstage Alzheimer's drugs that could dramatically reshape the firm's growth prospects if successful.

Moat and Product Portfolio

Expiring Patents

Product:		Forteo
Composition:		biologic (recombinant parathyroid hormone)
Economics:		—
Therapeutic Area:		osteoporosis
Patents/Generic Threats:		2018-19 U.S./international
2024 Sales	Morningstar	$463 million
	Consensus	$519 million
Market Model:		—

The complexity of the molecule will likely mean a more gradual decline in sales post patent protection in 2020. Also, branded competition from Radius and Amgen are weighing on Forteo sales.

Product:		Alimta
Composition:		small molecule (antifolate)
Economics:		single-digit royalty to Princeton
Therapeutic Area:		cancer
Patents/Generic Threats:		2017-22 U.S./2015-21 international
2024 Sales	Morningstar	$786 million
	Consensus	$501 million
Market Model:		—

The new immuno-oncology drugs will likely continue to take share, but combination usage with these drugs will drive sales. Also, we expect the 2022 patent to hold in the U.S. Generics have launched in Germany, but we expect this will be the only developed-market early launch for generic Alimta.

Product:		Cialis
Composition:		small molecule (PDE5)
Economics:		single-digit royalties to GSK
Therapeutic Area:		cardiovascular
Patents/Generic Threats:		2017 U.S./international
2024 Sales	Morningstar	$568 million
	Consensus	$374 million
Market Model:		—

Following the patent loss, sales should fall quickly, but a potential OTC launch with Sanofi could create a long-term tail.

Product:		Humalog
Composition:		biologic (insulin lispro)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2013 U.S.
2024 Sales	Morningstar	$2,518 million
	Consensus	$2,089 million
Market Model:		insulin (p.176)

Despite heavy pricing pressure in this market, this fast-acting insulin should still hold up reasonably well in the mature insulin market, aided partly by new higher dosages such as U-200. Sanofi launched Admelog, a biosimilar version of Humalog, in 2018, but Humalog's low net pricing (due to longstanding competition with Novo Nordisk's similar drug Novolog) will likely partially limit the pressure from Sanofi.

Inline Products

Product:		Humulin
Composition:		biologic (insulin isophane/regular)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		expired
2024 Sales	Morningstar	$1,260 million
	Consensus	$1,129 million
Market Model:		insulin (p.176)

This older biosynthetic human insulin is offered at half the price of modern insulins, but given the faster onset of modern insulins like Humalog, we expect Humulin to decline over the long term.

Product:		Jardiance
Composition:		small molecule (SGLT2)
Economics:		jointly developed with Boehringer Ingelheim
Therapeutic Area:		diabetes
Patents/Generic Threats:		2025+ U.S.
2024 Sales	Morningstar	$1,827 million
	Consensus	$1,927 million
Market Model:		noninsulin diabetes (p.175)

The SGLT-2 inhibitors target the kidneys by inhibiting the reabsorption of glucose back into the body. As a result, more glucose exits through urine, and blood sugar levels decrease, leading to more weight loss than other treatments (except GLP-1s). Also, the strong EMPA-REG outcomes data (38% reduction in cardiovascular death and 14% reduction in the expanded Mace primary endpoint) came ahead of data from competitors in the class, including J&J's Invokana (mid-2017 data showed 14% reduction in expanded Mace endpoint), Astra's Farxiga (September 2018 data showed statistically significant reduction in hospitalization for heart failure or cardiovascular death, but only trended well on MACE), and Merck's ertugliflozin (mid-2020E). Further, Jardiance is clean on ketoacidosis, acute kidney injury, and amputation. Line extension studies in reduced and preserved heart failure (data in late-2020), acute heart failure (data in mid-2021) and kidney disease (data in 2022) should support longer-term growth. However, functional studies in heart failure (walking tests) failed to show a benefit for Jardiance in reduced and preserved ejection heart failure.

Product:		Trulicity
Composition:		biologic (GLP-1)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2027 U.S. /2029 International
2024 Sales	Morningstar	$6,384 million
	Consensus	$6,616 million
Market Model:		noninsulin diabetes (p.175)

With weekly dosing and similar efficacy to once-daily Victoza (except in weight loss, where Victoza appears to still have an edge), Trulicity should both gain share and expand the GLP-1 class. However, head-to-head Sustain 7 data from Novo Nordisk with its weekly GLP-1 semaglutide (launched as Ozempic in second quarter 2018) showed an advantage in reducing A1c levels by 1.5% versus 1.1% on low dose and 1.8% versus 1.4% on high dose over Trulicity. Also, Ozempic statistically significantly lowered weight more than Trulicity. However, we expect the positive outcomes study Rewind (12% reduction in major cardiovascular events versus placebo, added to U.S. label in Feb. 2020) to support sales. Also, a high-dose Trulicity study showed A1c lowering (-1.7% and -1.9%) and weight reduction (-4kg and -4.7kg) at the 3mg and 4.5 mg dose which largely closes the gap versus Ozempic, but Novo Nordisk is running a high dose study with Ozempic with data likely at the end of 2020, which could show better results.

Product:		Cyramza
Composition:		biologic (VEGF)
Economics:		—
Therapeutic Area:		cancer
Patents/Generic Threats:		2026 U.S./2029 Europe/2026 Japan
2024 Sales	Morningstar	$1,309 million
	Consensus	$1,204 million
Market Model:		—

Despite immuno-oncology making significant strides in treating cancer, Cyramza's approvals in gastric, lung, and colorectal cancers should still have a place in the treatment pathway. Also, a phase 3 study in first-line EGFR non-small-cell lung cancer should support approval, but we doubt much update due to the strong clinical data from Tagrisso in this area.

Product:		Taltz
Composition:		biologic (IL-17)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		2026 (with biological protection to 2028) U.S./ 2031 Europe/ 2029 Japan
2024 Sales	Morningstar	$4,164 million
	Consensus	$2,908 million
Market Model:		psoriasis (p.166)

With leading efficacy (versus TNFs and Stelara) and no black-box warnings, Taltz should take market share from TNFs and Stelara in psoriasis (8 million in the U.S). While Taltz lost the first-mover advantage to Cosentyx, the gradual shift from TNFs should reduce the importance of the first to market advantage. Also, the approvals in psoriatic arthritis (1.6 million in the U.S.) in late 2017, axial spa (1.1 million in the U.S.) in 2019, and nonaxial spa in June 2020 (1.1 million in the U.S.) should drive longer-term sales. A head-to-head study versus Tremfya completed in 2019 with a 12-week endpoint that should showed superiority (PASI 100 of 41% for Taltz and 25% for Tremfya), but longer term data will be important, as Tremfya and other IL23s tend to perform better over a longer period of time.

Product:		Basaglar
Composition:		biologic (biosimilar basal insulin)
Economics:		small royalties to Sanofi
Therapeutic Area:		diabetes
Patents/Generic Threats:		--
2024 Sales	Morningstar	$1,497 million
	Consensus	$1,536 million
Market Model:		insulin (p. 176)

While Mylan's biosimilar Lantus will compete, we believe Eli Lilly's strong entrenchment in insulin production makes it the best positioned to gain market share with a biosimilar. Merck gained approval for its biosimilar Lantus called Lusduna Nexvue in July 2017 but decided to cancel commercial launches likely due to the pricing compression in the market. Mylan and Biocon's Semglee is approved in Europe and could reach the U.S. market in late 2020 (approved in June 2020).

Product:		Verzenio/Abemaciclib
Composition:		small molecule (CDK 4/6)
Economics:		—
Therapeutic Area:		cancer
Patents/Generic Threats:		2029 Global (with potential extensions)
2024 Sales	Morningstar	$2,612 million
	Consensus	$2,106 million
Market Model:		non-HER2+ Breast cancer (p.183)

While entering the CDK 4/6 market after both Pfizer and Novartis, Verzenio's ability to hit brain tumors and fewer side effects with anemia should allow it to gain close to 15% of the HER2-negative breast cancer market. The positive overall survival benefit (HR of 0.76) is solid but slightly worse than Novartis' Kisqali. However, Pfizer's Ibrance has yet to show a positive overall survival benefit, potentially opening up the door to competition from Verzenio. Importantly, the drug showed successful data in the high risk (30% of the market) adjuvant setting, likely making it the first CDK 4/6 into this large opportunity (doubling the market size from just the metastatic setting). A unique opportunity in the HER2+ segment (15-20% of the breast cancer market) could open up based on phase 2 monarcHER read out in 2019, but a Herceptin/chemo comparator is no longer the standard of care to beat in this indication (Perjeta combinations are favored).

Product:		Olumiant/Baricitinib
Composition:		small molecule (JAK1/2)
Economics:		royalties up to 20% to Incyte
Therapeutic Area:		RA
Patents/Generic Threats:		2029-33 (not including patent extensions)
2024 Sales	Morningstar	$1,529 million
	Consensus	$1,237 million
Market Model:		RA (p.167), atopic dermatitis (p.164)

With efficacy data similar to (slightly better than) Pfizer's JAK inhibitor Xeljanz and a cleaner side effect profile, Olumiant is likely to see well over $1 billion in peak sales. While the drug gained approval in Europe and Japan in early 2017, the FDA asked for more safety data (largely on VTE risks) and finally approved the drug in June 2018, but only the less effective 2 mg dose (not the 4 mg dose). Additionally, while other JAK inhibitors are targeting several indications outside of RA, Olumiant is leading in development for atopic dermatitis, with phase 3 data showing improvement over placebo but not as good as Sanofi's Dupixent (in cross trial comparisons). The drug was filed for atopic dermatitis in early 2020. The drug is also in development for lupus with phase 3 data expected by 2021. Phase 2 lupus data showed 67% resolution of lupus related arthritis or rash versus 53% for placebo—not great data, but there not many treatment options for lupus. Additionally, the drug is in development for alopecia areata with phase 3 data expected in 2022.

Product:		Emgality/galcanezumab/LY2951742
Composition:		biologic (CGRP)
Economics:		—
Therapeutic Area:		migraine/cluster headache
Patents/Generic Threats:		2033 Global
2024 Sales	Morningstar	$1,211 million
	Consensus	$1,256 million
Market Model:		migraine (p.178)

The phase 3 data looks fairly similar to other CGRP drugs and Emgality's approval in September 2018 is slightly behind Amgen/Novartis' Aimovig (approved by the FDA in May 2018) and inline with Teva's Ajovy (approved in September 2018). Emgality holds some slight differentiation with 100% migraine free levels in the label. Also, Emgality failed in chronic cluster headache, but the drug has shown positive data in episodic cluster headaches (more rare form of migraine at close to only 1% of all migraines) and Eli Lilly gained approval in this setting in mid-2019.

Product:		Reyvow/Lasmiditan
Composition:		Small molecule/5HT-1f
Economics:		—
Therapeutic Area:		acute migraine
Patents/Generic Threats:		
2024 Sales	Morningstar	$535 million
	Consensus	$364 million
Market Model:		migraine (p.178)

Eli Lilly gained the drug through the $1 billion acquisition of CoLucid Pharmaceuticals. Following two positive phase 3 studies and positive safety data, Eli Lilly filed the drug in late 2018 and gained approval in late 2019. The drug is similar to triptans but doesn't appear to have the same level of cardiovascular concerns. In phase 3 studies, the 200mg dose of the drug nearly tripled the percentage of triptan nonresponders who became pain free two hours after dosing, relative to placebo (in pooled data from Spartan and Samurai). There are close to 6 million patients on treatment for acute migraine in the U.S. with close to 40% of current patients not receiving a successful treatment and with the drug priced at $600 for eight tablets (100mg), we expect the drug to peak at less than $1 billion in annual sales.

Moat Trend and Product Pipeline

Product:		Tanezumab
Composition:		biologic (anti-NGF)
Economics:		50/50 profit split with Pfizer
Therapeutic Area:		pain
Launch Year/Probability:		2020/30%
2024 Sales	Morningstar	$632 million
	Consensus	$281 million
Market Model:		—

The two FDA clinical holds and J&J's 2016 decision to discontinue its NGF development program highlight the risks associated with this class of drugs and have led to close to zero in consensus sales expectations for the drug class, but the hold concerns have been addressed by further investigation. The phase 3 data have shown solid efficacy at high doses, but side effects of joint replacements (2% for placebo versus 4%-7% for tanezumab) and rapidly progressing osteoarthritis (0% versus 1%-2%) are concerning. Long term data in osteoarthrosis showed mixed data with positive efficacy with the 5mg dose (with worse side effects) and poor efficacy with the 2.5mg dose. The FDA and EMEA accepted the filing of the 2.5mg dose in March 2020. While we are concerned the FDA will not approve the drug based on the clinical data, we expect the drug will be widely used if approved given the limited options for pain management.

Product:		Retevmo/Selpercatinib/Loxo-292
Composition:		small molecule (RET cancers)
Economics:		bought Loxo for $8B for the drug and for TRK drug Loxo-195
Therapeutic Area:		cancer
Launch Year/Probability:		2020/100%
2024 Sales	Morningstar	$590 million
	Consensus	NA
Market Model:		—

Loxo-292 has shown overall response rates of 64-85% in highly refractory lung cancer patients and 69-73% response rates in thyroid cancer patients. The FDA approved the drug in May 2020. Eli Lilly mentioned close to 20% of patients were being tested for RET mutations as of mid/late 2019. RET mutations happen in 2%-3% of lung cancer patients and 10-20% in thyroid cancer patients and with a price point at $20,600 per month, the drug should be a major drug. Confirmatory phase 3 studies in lung and thyroid should report in 2023. On the competitive landscape, Blueprint Medicines filed a RET inhibitor pralsetinib with the FDA and could challenge Eli Lilly here.

Product:		Mirikizumab
Composition:		biologic (IL-23)
Economics:		—
Therapeutic Area:		psoriasis, ulcerative colitis and Crohn's
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	$775 million
	Consensus	$610 million
Market Model:		psoriasis (p.166), UC/Crohn's (p.168)

Mirikizumab should report phase 3 data in psoriasis (2020, first of two phase 3 studies reported positive data), ulcerative colitis (2021) and Crohn's disease (2022), but these studies might be delayed due to the coronavirus pandemic. The drug looks fairly similar to J&J's Tremfya and AbbVie's IL-23 drug risankizumab, but mirikizumab could be first to market in ulcerative colitis. However, Eli Lilly has flagged the drug as potentially facing clinical trial delays due to the coronavirus disruptions in gastro indications.

Product:		Tirzepatide
Composition:		biologic (GIP/GLP1)
Economics:		
Therapeutic Area:		diabetes
Launch Year/Probability:		2022/60%
2024 Sales	Morningstar	$475 million
	Consensus	$1,088 million
Market Model:		noninsulin diabetes (p.175)

Tirzepatide is a once-weekly dual incretin drug, hitting both GIP and GLP1. Phase 2 data in late 2018 showed excellent A1c and weight-lowering potential, significantly outperforming Trulicity at 26 weeks (more than doubling the treatment efficacy) with similar side effects. Phase 3 Surpass studies, including a comparison to Ozempic, should begin to read out in 2020, with cardiovascular outcomes data expected in 2025. The drug is also in a phase 3 obesity study (data in 2022). Also, a phase 2 study was recently started in NASH (data expected in 2022).

Product:		Lebrikizumab
Composition:		biologic (IL13)
Economics:		Bought Dermira for $1.1 billion for the drug
Therapeutic Area:		atopic dermatitis
Launch Year/Probability:		2022/70%
2024 Sales	Morningstar	$900 million
	Consensus	$290 million
Market Model:		atopic dermatitis (p. 164)

While the drug holds a slightly similar mechanism of action as Dupixent, lebrikizumab failed late stage studies in asthma, but looks well positioned in atopic dermatitis. Strong phase 2 data looks similar to Dupixent in atopic dermatitis. Phase 3 atopic dermatitis should be ready by late 2021.

Product:		Zagotenemab
Composition:		biologic (Tau)
Economics:		
Therapeutic Area:		Alzheimer's
Launch Year/Probability:		2025/10%
2024 Sales	Morningstar	Not meaningful
	Consensus	NA
Market Model:		Alzheimer's (p. 180)

The tau theory could support this drug, but little early data is available. Phase 2 data should provide more clarity in late 2020.

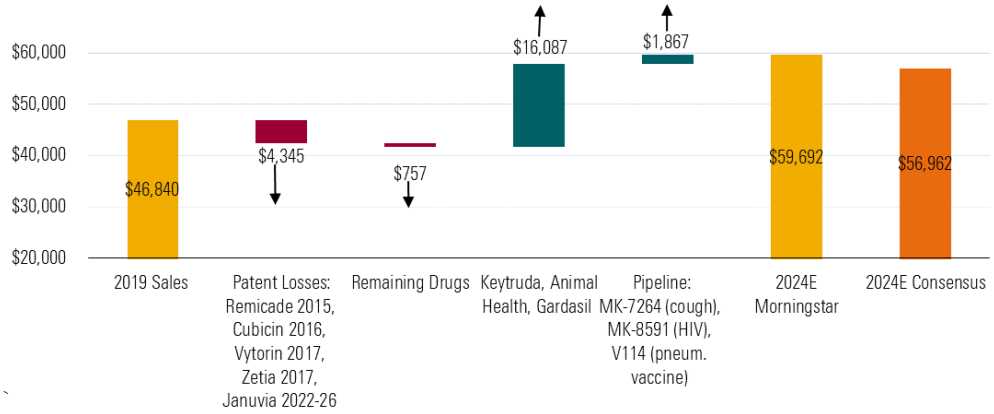
Product:		Donanemab
Composition:		biologic (N3PG)
Economics:		
Therapeutic Area:		Alzheimer's
Launch Year/Probability:		2025/10%
2024 Sales	Morningstar	Not Meaningful
	Consensus	
Market Model:		Alzheimer's (p. 180)

The drug has very strong plaque clearing potential so while a long shot, it could transform Alzheimer's treatment. Phase 2 data is expected in early 2021.

Merck MRK

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$100.00	0.80	Medium	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports and DrugAnalyst/S&P Cap IQ for consensus.

Keytruda, Gardasil, and Animal Health Should Offset Mature Drug Declines

Expiring Patents

Merck's diabetes drug Januvia will likely face the largest generic pressure over the next five years. While the drug is already facing pricing pressure from payers, we expect this will increase substantially by 2023 due to generic competition.

Inline Products

Keytruda is the major driver of growth with leadership in the lung cancer market. Gardasil, while late it its lifecycle, should post strong gains as payors are seeing the strong benefits of increased use for entire populations. Also, the vaccine structure should mean very limited generic pressure. Partnered drugs Lynparza and Lenvima in cancer should also provide steady gains based on strong clinical data. Also, the animal health business is well positioned for steady gains in a mature industry.

Pipeline

Merck has been very successful with developing new indications for Keytruda, and we believe new indications in adjuvant hold significant potential. However, the remaining pipeline looks fairly weak and needs replenishment. Drugs like HIV (MK-8591) and pneumococcal vaccines (V114) look interesting, but since they are entering such competitive spaces, we are skeptical the drug sales will be meaningful.

Moat and Product Portfolio

Expiring Patents

Product:		Zetia/Vytorin
Composition:		small molecule (cholesterol inh)
Economics:		-
Therapeutic Area:		cholesterol lowering
Patents/Generic Threats:		2017 U.S./2017-19 EU/2019 Japan
2024 Sales	Morningstar	$253 million
	Consensus	$257 million
Market Model:		—

These small-molecule drugs will decline quickly following the patent losses in different geographies of the world.

Product:		Remicade
Composition:		biologic (TNF)
Economics:		source product from J&J for Europe
Therapeutic Area:		immunology
Patents/Generic Threats:		2012-15
2024 Sales	Morningstar	$121 million
	Consensus	$121 million
Market Model:		RA (p.167), UC/Crohn's (p.168), psoriasis (p.166)

Biosimilar pressure in Europe has been growing since 2015 and future annual declines over 20% are likely. However, a significant portion of the damage is already done with the biosimilars gaining over 40% of the volume share in Europe.

Product:		Januvia/Janumet
Composition:		small molecule (DPPIV)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2022 U.S., EU/2025-26 Japan
2024 Sales	Morningstar	$2,250 million
	Consensus	$1,284 million
Market Model:		noninsulin diabetes (p.175)

Januvia's strong outcomes study Tecos (no increase in heart failure) ensures a place in the diabetes treatment path for Januvia and sets up a strong combo with SGTL2 drug ertugliflozin (partnered with Pfizer and approved as Steglatro in early 2018). The heart failure risks seen with Astra's Onglyza (Savor study) and Takeda's Nesina (Examine study) also help differentiate Januvia. However, the solid data from the outcome study Carolina for Eli Lilly's DPPIV Tradjenta (in early 2019) sets up a stronger competitor to Januvia.

Inline Products

Product:		Keytruda
Composition:		Biologic (PD-1)
Economics:		6.5% royalty to BMY/Ono
Therapeutic Area:		cancer
Patents/Generic Threats:		2028 U.S./EU/China, 2032 Japan
2024 Sales	Morningstar	$24,400 million
	Consensus	$21,534 million
Market Model:		immuno-oncology (p.181)

Keytruda has racked up several approvals in cancer, but the most important for our sales forecast is the first-mover advantage in non-small-cell lung cancer in the U.S. While competitive data from Bristol (minor threat) and Astra (data in 2021) in first-line non-small-cell lung cancer along with Roche's Tecentriq (approved in late 2018) will increase pressure on Keytruda, Merck's early launch (2016) in this large market will likely allow Keytruda to gain the majority of share in the immuno-oncology market. Recent approvals in renal, esophageal and refractory small cell lung cancer and more reimbursement in international markets (first line NSCLC: Spain and Italy 4Q19, France: September 2019, UK: April 2019, Germany September 2018) should help drive sales. Also, new dosing at once every six weeks (approved by the FDA in April 2020), up from every four weeks should help (most PDL1 drugs are dosed every four weeks).

While not all data has been positive (Keytruda failed in certain breast, bladder, gastric and liver cancer studies and didn't show an OS benefit in small cell lung cancer), we expect several more additional indications to drive sales:

2020-2022 key events:
2020: Approval expected in triple negative breast cancer (based on strong KN-355 results at ASCO, PFS HR of 0.65), Kidney (KN-581), Approved in June 2020 in colorectal with MSI high, first line (KN-177 showed good data with PFS HR of 0.60 at ASCO in May 2020)
2021: NSCLC adjuvant (KN-091), Head and Neck adjuvant (KN-412 and KN-689), Prostate (KN-921), Esophageal first line (KN-590), Triple negative breast cancer adjuvant/neoadjuvant (KN-522)
2022: Renal adjuvant (KN-716), Stage II Melanoma adjuvant (KN-716)

Product:		Gardasil
Composition:		biologic/vaccine
Economics:		10-18% royalties to GSK
Therapeutic Area:		HPV
Patents/Generic Threats:		2028 U.S./international
2024 Sales	Morningstar	$6,003 million
	Consensus	$5,810 million
Market Model:		—

Gardasil should continue to dominate the HPV market with little competition. The ongoing launch in China (100-150 million women eligible to receive vaccine under current indication) and the expanded age range of up to 45 years old in the U.S. should help drive further growth (ACIP recommendation for expanded age group occurred in June 2019). A study from Australia showed that a vaccination rate of 80-90% could lead to almost eradication of cancer stemming from HPV, which has driven renewed interest in the vaccine. With about 3% of the global population using the vaccine, there is room for expansion. New manufacturing should come online by 2023-2024 that should double supply. Also, the vaccine fully lapped the shift to 2 doses from 3 in mid-2018.

Product:		Lynparza
Composition:		small molecule (PARP)
Economics:		50% of profits to Astra
Therapeutic Area:		cancer
Patents/Generic Threats:		2028 U.S./2021-27 international
2024 Sales	Morningstar	$1,302 million
	Consensus	$1,216 million
Market Model:		—

With approvals in first- and second-line ovarian cancer, breast cancer, and strong first-line ovarian cancer data in Solo-1 (PFS HR of 0.30), the drug is already well positioned in these BRCA mutated patients (15% of all ovarian, 2%-10% of breast)20.

The FDA approval in early 2020 for pancreatic cancer followed by EU approval in July 2020 (4-7% have BRCA mutations)21 with strong data (PFS HR of 0.53) adds more potential. The PAOLA-1 study with Avastin (FDA approved in May 2020) adds more first-line ovarian patients (BRCA and HRD+, 65% of the market, but not HRD- patients where competitor Zejula from GSK will likely have an advantage) with strong PFS HR data (0.31-0.33 in BRCA or HRD+ versus data seen from Glaxo's competitive drug Zejula 0.40-0.43). Also, Profound (2L prostate cancer data reported Aug. 2019 and FDA approved in May 2020) had solid data (PFS HR of 0.34 and a positive OS benefit in BRCA and PFS HR of 0.49 in homologous recombination repair (HRR) mutations with a survival benefit) and should add more potential patients in all homologous recombination repair HRR patients (1-2% of prostate patients have a BRCA mutation, which is a subset of HRR that represents close to 20-30% of prostate cancers)2223. Note HRD is short for HRR deficiency.

With developed markets and China having large numbers of treated patients in ovarian (84,000 first line of which 18,000 have BRCA mutation), breast (45,000 BRCA), pancreatic (10,000), and prostate cancers (1,000 BRCA 2nd line and 10,000 HRR), the drug holds strong potential and is priced at close to $150,000 a year in the U.S.24

Additional phase III studies with Zytiga in "all comers" prostate cancer (data in 2021) and as monotherapy in adjuvant HER2- BRCA breast cancer (data in 2022) could add to the label. Data in lung cancer should ready in 2024. Other approved PARPs Rubraca and Zejula appear to have similar efficacy and safety but look behind Lynparza on timing of approvals.

Product:		Lenvima
Composition:		Small molecule receptor tyrosine kinase (RTK) inhibitor
Economics:		50/50 split with Eisai plus milestone payments to Eisai
Therapeutic Area:		cancer
Patents/Generic Threats:		2025/2026 (extensions should add years)
2024 Sales	Morningstar	$843 million
	Consensus	$1,018 million
Market Model:		

With recent approvals in liver, thyroid, and renal cell cancer, Lenvima is already well positioned for growth. Combination data with Keytruda holds potential in renal cell cancer (KN-581, data in 2020) and lung cancer (LEAP-006, data in 2023). Several monotherapy studies are ongoing in endometrial, skin, lung, bladder and head and neck cancer.

20 BRCA mutation in high grade epithelial ovarian cancers, Manchana, Tarinee et al., August 2019, Dana Farber Cancer Institute, Rana, Huma, June 2019.

21 National Cancer Institute, Trial Highlights Complexities of Targeted Therapy for Pancreatic Cancer

22 Androl, Asian The role of BRCA1 and BRCA2 in prostate cancer, 2012.

23 Li et al. Homologous recombination in DNA repair and DNA damage tolerance. Cell Research, 2008.

24 Data Monitor, Decision Resources Group, Kantar Health and AstraZeneca

Product:		Steglatro/Ertugliflozin Steglujan/Ertugliflozin+Januvia
Composition:		small molecule (SGLT2)
Economics:		40% of profits to Pfizer
Therapeutic Area:		diabetes
Patents/Generic Threats:		2031 U.S.
2024 Sales	Morningstar	$494 million
	Consensus	$509 million
Market Model:		noninsulin diabetes (p.175)

Despite ertugliflozin's late entry into the SGLT-2 market, the development partnership with Pfizer (60% of profits to Merck/40% to Pfizer) should facilitate a fixed-dosed combination with Merck's market leading DPPIV drug Januvia. With the majority of the DPPIV market controlled by Januvia, we expect the combination of Januvia and ertugliflozin to drive market share gains despite entering the market following three established players. However, in the outcomes study (VERTIS), the drug was only non-inferior to placebo not better, which likely means the drug will have a hard time versus other SGLT2 drugs that showed a cardiovascular benefit.

Product:		Bridion
Composition:		small molecule
Economics:		
Therapeutic Area:		Anesthesia reversal
Patents/Generic Threats:		2023-2026
2024 Sales	Morningstar	$1,517 million
	Consensus	$1,369 million
Market Model:		

Bridion is a reversal agent used in anesthesia, which offers a quicker mode of action. The drug took a long time to work through the approval process by regulators, showing the complexity of the drug. We expect more limited generic threats base on the drug's complexity in administration.

Product:		Pifeltro/Doravirine Delstrigo/Doravirine+lamivudine+Viread
Composition:		small molecule (NNRTI)
Economics:		-
Therapeutic Area:		HIV
Patents/Generic Threats:		
2024 Sales	Morningstar	$162 million
	Consensus	$306 million
Market Model:		HIV (p.190)

Phase 3 studies have shown favorable noninferior data on efficacy (84% versus 80% for Prezista and 84% versus 81% for Sustiva). Also, safety looks clean, with superior lipid profiles and fewer neuropsychiatric side effects versus Sustiva-based regimens. However, the strong efficacy of the integrase class may limit the potential for this strong NNRTI in the HIV market.

Moat Trend and Product Pipeline

Product:		V114
Composition:		vaccine
Economics:		—
Therapeutic Area:		pneumococcal disease
Launch Year/Probability:		2021/70%
2024 Sales	Morningstar	$420 million
	Consensus	$593 million
Market Model:		—

While V114 covers two more serotypes of pneumococcal disease than Prevnar 13, Merck appeared to have trouble selecting the optimal dose and several phase 2 studies have completed over the past five years with mixed efficacy data on infants. In 2018, Merck started the majority of its phase 3 program (seven phase 3 studies) that should read out between 2020 and 2021 and the first two adult phase 3 studies posted good topline data in June 2020. Also, Pfizer is working on a next-generation Prevnar that could cover potentially 20 serotypes. Merck has an earlier stage vaccine (V116) focused on more coverage (not fully disclosed how many serotypes).

Product:		Gefapixant/MK-7264
Composition:		small molecule (P2X3)
Economics:		minor milestones to Afferent
Therapeutic Area:		chronic cough
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	$173 million
	Consensus	$327 million
Market Model:		—

In a phase 2 study (253 patients), MK-7264 reduced cough frequency (coughs/hour) by 37% versus placebo. Taste interference was the main side effect. Phase 3 data posted positive topline data in March 2020 with more details to come at a scientific conference. However, only the 45 mg. dose (twice daily) worked, as the 15 mg. dose didn't show a benefit. The prevalence of chronic cough is estimated at 10% of U.S. adults.

Product:		Islatravir/MK-8591
Composition:		small molecule NRTTI
Economics:		-
Therapeutic Area:		HIV
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	$389 million
	Consensus	$726 million
Market Model:		HIV (p.190)

Early data in 2019 in 12 patients indicated than a plastic rod implant of this novel drug could protect patients from infection for one year. Merck started a phase 2 for a once-monthly oral PrEP regimen in Sept 2019. Merck has also experimented with using the drug as part of a two-drug treatment regimen (with doravirine), but a Phase 2b comparison versus the relatively weak comparator Delstrigo showed similar efficacy and higher virologic failure rates (5.6% versus 3.2%). We expect the drug could be tested in different combinations, but creating a once-weekly treatment regimen could be challenging. Phase 3 data should report out in 2021-2023.

Product:		V160
Composition:		vaccine
Economics:		-
Therapeutic Area:		CMV virus
Launch Year/Probability:		2025/20%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	$88 million
Market Model:		

With very limited data on the vaccine so far, the phase 2 data expected in May 2021 will be critical for the vaccine's potential success.

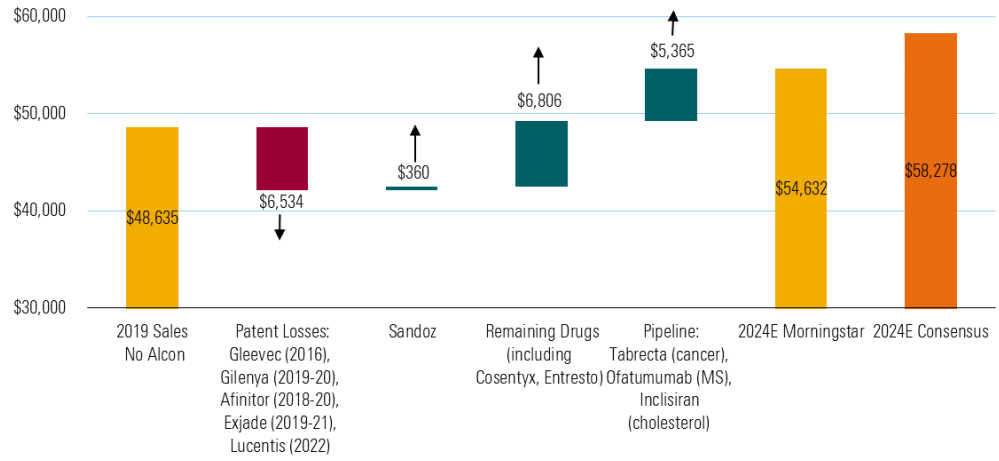
Product:		MK-6482
Composition:		Small molecule (HIF-2 inhibitor)
Economics:		-
Therapeutic Area:		Cancer (rare mutations)
Launch Year/Probability:		2025/20%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	$108 million
Market Model:		

Data at ASCO 2020 showed an objective response rate of 28% in the rare von Hippel Lindau renal cancer (10,000 cases in the U.S.). While the data looks encouraging, the limited number of patients leads us to believe this drug will not be very meaningful to Merck's sales.

Novartis NVS

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$91.00	0.97	Low	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports; DrugAnalyst/S&P Cap IQ for consensus.

Novartis Is Losing Entrenched Cancer Positioning Because of Patent Losses

Expiring Patents

Patent losses on key cancer drugs Afinitor (2018-20) will hurt Novartis' entrenchment in cancer, but several recently launched new oncology drugs should support the firm's leading position in oncology. Also, while we still project major generic competition to MS drug Gilenya in 2021, longer-term patents (out to December 2027) could hold off generic competition.

Inline Products

Cosentyx and Entresto hold major potential with peak annual sales over $8 billion (collectively) based on strong efficacy, minor side effects, and first-mover advantages. Several recently launched drugs in rare diseases, cancer, and multiple sclerosis set up strong, steady long-term growth.

Pipeline

The firm's focus on areas of unmet medical need (except in respiratory disease) should set the firm up well to deal with patent losses over the long term. We remain most bullish on cholesterol-lowering drug inclisiran and multiple sclerosis drug ofatumumab.

Moat and Product Portfolio

Expiring Patents

Product:		Gleevec
Composition:		small molecule (TKI)
Economics:		—
Therapeutic Area:		cancer
Patents/Generic Threats:		2016 U.S./EU, 2014 Japan
2024 Sales	Morningstar	$395 million
	Consensus	$466 million
Market Model:		—

Rapid declines should continue for this relatively simple compound, and we expect almost $1 billion in lost sales due to generic competition over the next five years.

Product:		Lucentis
Composition:		biologic (VEGF)
Economics:		Ex U.S. rights, 10% to Roche
Therapeutic Area:		ophthalmology
Patents/Generic Threats:		2018-22
2024 Sales	Morningstar	$1,036 million
	Consensus	$1,104 million
Market Model:		—

Regeneron/Bayer's Eylea has bimonthly dosing (or quarterly for over half of patients) and stronger efficacy in wet AMD, leading to market losses for the once-monthly Lucentis. Also, cost-conscious markets are opting for low-cost reformulated Avastin over Lucentis (but this trend has largely stabilized). However, Novartis' Beovu holds the potential for quarterly dosing, which may drive market share gains. Additionally, the biologic structure and administration into the eye will create tough hurdles for biosimilars. Beyond wet age-related macular degeneration, the drug is also approved for retinal vein occlusion, diabetic macular edema, diabetic retinopathy, and myopic choroidal neovascularization.

Product:		Afinitor
Composition:		small molecule (mTOR inhibitor)
Economics:		-
Therapeutic Area:		cancer
Patents/Generic Threats:		2019
2024 Sales	Morningstar	$214 million
	Consensus	$223 million
Market Model:		—

With approvals in HER2- breast cancer, neuroendocrine tumors of pancreatic, gastrointestinal or lung origin, and renal cancer, Afinitor carries a wide label that is facing competition from immuno-oncology drugs. Following the 2019 patent loss, the drug should decline rapidly, losing over $1 billion over the next five years.

Product:		Gilenya
Composition:		small molecule (sphingosine 1-ph rec.)
Economics:		20% to Mitsubishi Tanabe
Therapeutic Area:		MS
Patents/Generic Threats:		2019-20 U.S./2021 EU
2024 Sales	Morningstar	$808 million
	Consensus	$1,054 million
Market Model:		MS (p.177)

While getting later in the life cycle for the drug, the convenient oral dosing, strong efficacy, and manageable cardiovascular side effects should help the drug keep market share. However, Novartis won an inter partes review that validated a dosing patent until December 2027, which may hold off generic competition for several more years, but we are still modeling U.S. generic competition beginning in 2021. The dosing patent is under appeal by generic firms and verdicts should read out in 2020. There is an additional patent regarding the treatment of MS by identifying a virus, but this patent looks weak. Also, competition from Roche's Ocrevus (launched 2017), J&J's ponesimod (2021 launch, also S1P-targeting), Bristol's Zeposia (2020 launch with similar mechanism of action as Gilenya, but fewer cardiovascular side effects) as well as Novartis' next-generation MS drugs Mayzent and ofatumumab will likely take share.

Inline Products

Product:		Tasigna
Composition:		small molecule (TKI)
Economics:		-
Therapeutic Area:		cancer
Patents/Generic Threats:		2024 U.S./2023 OUS
2024 Sales	Morningstar	$531 million
	Consensus	$752 million
Market Model:		—

While Tasigna has shown a minor benefit over Gleevec, we expect it to be reserved for current patients and Gleevec failures because of the low price of generic Gleevec.

Product:		Ilaris
Composition:		biologic (IL1B)
Economics:		-
Therapeutic Area:		wide ranging
Patents/Generic Threats:		2024 U.S./2021 EU/Japan
2024 Sales	Morningstar	$1,992 million
	Consensus	$922 million
Market Model:		—

While Ilaris is approved for several indications, the patient sizes are small, as most indications target rare diseases. The opportunity set for the drug has changed following the successful Cantos study. While the drug showed a benefit in the study's primary focus of cardiovascular disease (15% risk reduction in MACE), the potentially more important outcome is the benefit in preventing cancer (51% risk reduction in cancer overall and 77% reduction in lung cancer death). The non-small-cell lung cancer studies, Canopy N (phase 2 adjuvant, data in 2021-22), Canopy-1 (first line with Keytruda, data in 2021) and Canopy-2 (2nd line, data in 2021) are needed to support this important new indication. Also, an adjuvant lung cancer study should complete in 2022.

Product:		Entresto
Composition:		small molecule (neprilysin)
Economics:		-
Therapeutic Area:		Cardiovascular
Patents/Generic Threats:		2023 U.S./2026 EU
2024 Sales	Morningstar	$1,971 million
	Consensus	$4,238 million
Market Model:		—

With close to 10 million people diagnosed in developed markets with the type of heart failure studied (reduced ejection fraction, meaning the heart muscle does not contract effectively and less oxygen-rich blood is pumped out to the body) and a high treatment rate (over 80%), we expect the drug to generate peak sales in excess of $3 billion annually. Also, the market potential would double if the drug gained approval in preserved heart failure, but we doubt the drug will gain approval due to the failed Paragon study. (Preserved ejection fraction: heart muscle contracts normally but the ventricles do not relax as they should during ventricular filling.) Another indication is post-acute myocardial infarction (Paradise-2020 data, but smaller opportunity). The later Japanese approval in June 2020 could give the drug more runway in this important market.

Product:		Cosentyx
Composition:		biologic (IL17)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		2027 U.S./2025 international
2024 Sales	Morningstar	$5,322 million
	Consensus	$5,608 million
Market Model:		psoriasis (p.166)

With no black-box warning, approvals in psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis, convenient dosing (once every four weeks), and superior efficacy to Enbrel and Stelara, Cosentyx is poised for peak annual sales over $5 billion. The competitive threat from J&J's IL-23 Tremfya (dosed once every eight weeks) is heightened due to a J&J head-to-head 1,000 patient psoriasis study (Eclipse) that showed superior PASI 90/100 data for Tremfya at 48 weeks. However, the data was not better at 12 weeks, which supports Cosentyx's faster onset of action. Although the side effect profile for Tremfya may include fewer challenges related to IBD, we don't expect a major impact from Tremfya on Cosentyx. The IL-17 class looks better positioned in axial spa (ankylosing spondylitis/joint damage on X-ray and non-axial spa/joint damage not on X-ray) over the IL-23s. The Prevent study in nonradiographic Spa showed positive topline data in late 2019. Additionally, Cosentyx and Eli Lilly's IL-17 Taltz look very similar, but there are potentially unfavorably higher levels of immunogenicity with Taltz. Also, UCB's bimekizumab (another IL17, but targets the sub 17F in addition to 17A, Cosentyx and Taltz target 17A only) should have head-to-head data versus Cosentyx in 2020.

Product:		Kymriah
Composition:		biologic (CD19, targeting 4-1bb)/CART
Economics:		-
Therapeutic Area:		cancer
Patents/Generic Threats:		2031
2024 Sales	Morningstar	$1,166 million
	Consensus	$1,030 million
Market Model:		NHL (p. 185)

With strong data in refractory ALL (83% overall remission rate), the drug should do well in this patient population despite the complexity of CAR-T cell administration. Also, the strong data in Juliet (refractory DLBCL) showing complete responses of 43% versus an 8% historical control rate supported approval in the U.S. (May 2018) and Europe (June 2018), but the data was slightly worse than Gilead's Yescarta, although the Kymriah patient population looked sicker at the start of the study. Priced at $475,000, the market potential is significant despite small overall patient numbers in ALL (6,000 U.S. incidence rate) and DLBCL (21,000). Also, studies in second-line DLBCL, and FL (filing expected in 2021) are progressing. However, Gilead's Yescarta is also approved in DLBCL and Bristol's liso-cel has a November 2020 PDUFA.

Product:		Kisqali
Composition:		small molecule (CDK 4/6)
Economics:		royalties to Astex
Therapeutic Area:		cancer
Patents/Generic Threats:		2027-2031
2024 Sales	Morningstar	$1,609 million
	Consensus	$1,407 million
Market Model:		non-HER2+ breast cancer (p.183)

Despite strong data for breast cancer, we only expect 10% market share in the metastatic disease setting and 20% market share in the adjuvant setting, leading to peak sales of $3 billion, due to Kisqali's late entrance following Pfizer's Ibrance. Also, EKG monitoring (to make sure to avoid QT prolongation seen in studies) along with some liver toxicity issues may slow adoption. However, the good data in the premenopausal patient group (less than 20% of breast cancer) could open more opportunity. Also, the positive overall survival data looks the strongest with Kisqali, which could help offset its late entrance into the market.

Product:		Xiidra
Composition:		Small molecule (LFA-1 inhibitor)
Economics:		$3.4B upfront to Takeda followed by up to $1.9B in milestones
Therapeutic Area:		Dry eye
Patents/Generic Threats:		2024
2024 Sales	Morningstar	$571 million
	Consensus	$890 million
Market Model:		--

Acquired in May 2019 to help complement Novartis' growth ophthalmology drug business, the drug treats signs and symptoms of dry eye, which helps differentiate the drug from Allergan/AbbVie's competing drug Restasis, which just treats the signs of dry eye. With generic competition for Restasis launching in 2020, Xiidra will need to showcase the symptoms (lowering inflammation more quickly) to keep market share from slipping to cheap generic Restasis. European approval is less likely given concerns from the European regulators. Additionally, the company has a molecule in late stage development (ECF843) that could extend this franchise.

Product:		Aimovig (erenumab)
Composition:		biologic (CGRP)
Economics:		AMGN Japan/Copromote U.S./Novartis ROW
Therapeutic Area:		migraine
Patents/Generic Threats:		2031 U.S./2029 EU
2024 Sales	Morningstar	$720 million
	Consensus	$509 million
Market Model:		migraine (p.178)

Aimovig was approved in Europe in July 2018 as a first-in-class therapy for migraine prevention, but similar competition including Eli Lilly's Emgality (November 2018) and Teva's Ajovy (Sept. 2018) will make this a competitive market, and oral prevention competition from Allergan or Biohaven could reach the market as early as 2021. This CGRP receptor antibody appears to prevent migraines in both episodic and chronic migraine settings. In the phase 2b chronic migraine study, patients saw a 6.6-day reduction from baseline in the number of migraine days per month in the last four weeks of the study, in each Aimovig arm, versus a 4.2-day reduction in placebo arm. Amgen has also reported data from two phase 3 episodic migraine studies; Arise showed a 2.9-day reduction in monthly migraine days taking the 70 mg dose after 12 weeks, versus a 1.8-day reduction on placebo, and Strive showed a 3.2-to-3.7-day reduction for 70 mg-140 mg doses, versus a 1.8-day reduction on placebo. Aimovig's once-monthly subcu injection looks more appealing than Lundbeck's (IV), but potentially not as convenient as Teva's (quarterly subcu option).

Product:		Lutathera
Composition:		radioligand therapy
Economics:		bought AAA for $3.9B
Therapeutic Area:		Cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	$543 million
	Consensus	$1,014 million
Market Model:		—

Lutathera is a radioligand that gained approval in gastro-enteropancreatic neuroendocrine tumors in early 2018 due to an exceptionally strong improvement of 79% in progression-free survival over chemotherapy. However, the real potential for the drug is in late-stage prostate cancer, but the timeline is less clear in this indication.

Product:		Beovu/Brolucizumab/RTH258
Composition:		biologic (VEGF)
Economics:		-
Therapeutic Area:		Age-related macular degeneration
Patents/Generic Threats:		2033 Most markets
2024 Sales	Morningstar	$977 million
	Consensus	$1,186 million
Market Model:		—

In the key phase 3 studies Hawk and Harrier, Beovu was noninferior to market leader Eylea in age-related macular degeneration (AMD). Additionally, 52%-57% of Beovu patients were able to follow a 12-week dosing regimen versus eight-week dosing for Eylea (after loading doses for both). Beovu showed less retinal fluids, less fluid deep in the retina, and reductions in retinal thickness. Beovu was approved in Oct. 2019 (U.S) and Feb. 2020 (Europe) for AMD. Filings in diabetic macular edema (DME) and retinal vein occlusion (RVO) should occur in 2021 and 2023, respectively. Also, in contrast to Lucentis (where Novartis has only international rights), Novartis has global rights to Beovu. However, share gains over Bayer/Regeneron's Eylea could be difficult, and new competition from high-dose Eylea (allows for some patients to have only quarterly dosing), and Roche's port delivery of Lucentis could weigh on uptake. Also, vasculitis (inflammation) was reported in a small group of patients taking the drug shortly after launch, which could slow the drug's uptake. We expect several additional studies in AMD, DME and RVO over the next three years to largely reinforce the initial data. However, the Talon study has a superiority endpoint versus Eylea (data in 2020/2021) that we believe needs to show efficacy or it will be challenging for the drug to take share from Eylea.

Product:		Mayzent/BAF312/siponimod
Composition:		small molecule (S1P, sub units 1 and 5)
Economics:		—
Therapeutic Area:		Multiple sclerosis (MS)
Patents/Generic Threats:		2024 with extensions pending
2024 Sales	Morningstar	$930 million
	Consensus	$948 million
Market Model:		MS (p.177)

Mayzent reduced the risk of disability progression by 21% compared with placebo (p=0.013) in people with secondary progressive multiple sclerosis, a patient population with few treatment options. There are no other ongoing phase 3 studies. The FDA had asked for extension studies for more safety data, and Novartis had to finalize the manufacturing platform, so the filing was delayed until second quarter 2018 in the U.S. The drug was approved in the U.S. in March 2019 and in Europe in January 2020. Also, the mechanism of action is very similar to Bristol's Zeposia, but Zeposia is targeting the relapsing remitting patient population.

Product:		Piqray/Aleplisib BYL719
Composition:		small molecule (PI3K)
Economics:		
Therapeutic Area:		cancer
Launch Year/Probability		2020/70%
2024 Sales	Morningstar	$1,341 million
	Consensus	$1,319 million
Market Model:		—

The FDA approved the drug in May 2019, followed by CHMP positive opinion in May 2020. While the mechanism of action has shown mixed results (Gilead's Zydelig and Verastem's Copiktra have been relegated to later lines of leukemia and lymphoma treatment due to side effects), the phase 3 study Solar in second-line breast cancer showed a 35% improvement in progression free survival in HR+/HER2- patients with a PIK3CA mutation. This mutation occurs in close to 40% of HR+/Her2- breast cancer patients.

Product:		Adakveo/SEG101/crizanlizumab
Composition:		biologic (P-selectin)
Economics:		acquired Selexys ($665 million for rights)
Therapeutic Area:		sickle cell
Launch Year/Probability:		2019/80%
2024 Sales	Morningstar	$420 million
	Consensus	$647 million
Market Model:		—

Adakveo was approved by the FDA in Nov. 2019 and should gain approval in other parts of the world in 2020. The drug showed strong efficacy and reduced the annual rate of sickle cell-related pain crises by 45%. With 100,000 patients in the U.S. and the EU, prevalence is moderate, but with over 200,000 visits in the U.S. annually, patients need treatment options. Also, competitive therapies in gene editing are under investigation, which could make the space more crowded.

Product:		Zolgensma (AVXS-101)
Composition:		biologic (gene therapy)
Economics:		bought Avexis for $8.7B
Therapeutic Area:		spinal muscular atrophy (SMA)
Launch Year/Probability:		2019/90%
2024 Sales	Morningstar	$2,096 million
	Consensus	$2,035 million
Market Model:		—

Zolgensma is a gene therapy that requires one dose into the spinal canal to treat the rare disease of SMA. The drug looks more effective than Biogen's Spinraza, with at least 4 points of CHOP-INTEND improvement for 92% of patients at 1 month versus 71% for Spinraza (Endear study) at 14 months (we note that Endear enrolled older infants than the AveXis study, and that Spinraza's Nurture study in younger, presymptomatic patients showed near-normal CHOP INTEND scores over a two-year period, so efficacy may not be as differentiated). Roche's oral therapy risdiplam showed similar efficacy as Zolgensma, but we believe Roche will target older patients more effecitvely while Novartis will be more effective targeting infants with the ability to cure. Zolgensma was approved by the FDA in all types of SMA in May 2019, followed by Japan in March 2020 and Europe in May 2020. Type 1, 2 and 3 have 3,300, 12,000 and 8,200 patients in developed markets, respectively. With U.S. pricing at $425,000 per year for five years, the drug has blockbuster potential despite the small number of patients. One challenge for the drug is the intrathecal (through the spinal cord) dosing has been put on clinical hold by the FDA due to inflammation concerns, but we expect additional data will clear the dosing, which is important for older infants that need more of the drug than what an IV can deliver.

Moat Trend and Product Pipeline

Product:		Tabrecta/Capmatinib/INC280
Composition:		small molecule (MET)
Economics:		—
Therapeutic Area:		cancer
Launch Year/Probability:		2020/100%
2024 Sales	Morningstar	$300 million
	Consensus	$419 million
Market Model:		—

Phase 2 data from the Geometry study showed an overall response rate of 68% in first-line non-small-cell lung cancer and 41% in previously treated patients. While the study was small with only 97 patients, Novartis filed on the data in late 2019 and the FDA approved the drug in May 2020 along with a companion diagnostic. With close to 3%-4% of NSCLC patients (4,000 to 5,000 patients in the U.S. annually) having the MET mutation (according to Tong et. al in Clinical Cancer Resources), this drug would target a more limited number of patients, but at a price of close to $250,000 annually, the drug should drive significant sales. Merck KGaA has a competitive MET drug Tepmetko, but the drug has only been approved in markets outside the U.S.

Product:		Ofatumumab/OMB157
Composition:		biologic (CD20)
Economics:		12% to GSK
Therapeutic Area:		MS
Launch Year/Probability:		2020/80%
2024 Sales	Morningstar	$1,309 million
	Consensus	$1,742 million
Market Model:		MS (p.177)

The drug was filed in the U.S. and Europe in February 2020 and an FDA decision is expected by September 2020 and a decision in Europe by 2Q21 as some additional information was requested during the filing. Phase 3 data showed a reduction in relapse by 51% versus Aubagio. Also, in a phase 2 study, the drug led to over 90% reduction in T1 GdE lesions relative to placebo. The drug looks similar in efficacy as Ocrevus, which has a similar mechanism of action. However, ofatumumab binds to CD20 at a different spot, potentially increasing its potency relative to Ocrevus. Also, ofatumumab is dosed subcutaneously rather than IV for Ocrevus, which allows for better convenience and potentially slightly better efficacy.

Product:		Inclisiran
Composition:		Biologic (PCSK9)
Economics:		Bought Medicines company for $9.7B
Therapeutic Area:		Cholesterol
Launch Year/Probability		2021/95%
2024 Sales	Morningstar	$550 million
	Consensus	$1,097 million
Market Model:		—

While approved PCSK9 drugs (Amgen's Repatha and Sanofi/Regeneron's Praluent) have largely been commercial disappointments, this drug looks to offer the same level of efficacy with only two doses a year (compared to monthly or twice monthly). However, we believe the drug needs outcomes data (potentially as early as 2022), before the drug can gain commercial traction. The drug should likely gain approval in 2020 based on well accepted surrogate endpoints.

Product:		Enerzair/QVM149
Composition:		small molecule (LAMA+LABA+ICS)
Economics:		
Therapeutic Area:		asthma
Launch Year/Probability		2020/100%
2024 Sales	Morningstar	$306 million
	Consensus	$281 million
Market Model:		nonbiologic respiratory (p.170)

With Novartis outlicensing the rights to this drug in the U.S. to Sunovion, we are less bullish on its potential, well below management's guidance of over $1 billion in annual sales. Additionally, we don't see much differentiation with this triple-drug combination over competing drugs from Glaxo and Astra. However, with European approval in June 2020, the drug should reach the European market at a similar timeline as Glaxo in the asthma indication.

Product:		Spartalizumab/PDR001
Composition:		biologic (PD-1)
Economics:		
Therapeutic Area:		cancer
Launch Year/Probability		2021/80%
2024 Sales	Morningstar	$144 million
	Consensus	NA
Market Model:		immuno-oncology (p.181)

While this PD-1 drug is late to the immuno-oncology market, the combination potential with Novartis' BRAF and MEK inhibitors in BRAF+ melanoma should give the drug some potential with a phase 3 study in melanoma expect to complete in late 2020. However, we are skeptical the drug will reach over $1 billion in annual sales (guided by Novartis) as the drug is too late in many indications relative to competition, and we don't believe the drug has a superior efficacy profile.

Product:		Lu-PSMA-617
Composition:		radioligand therapy
Economics:		bought Endocyte for $2 billion
Therapeutic Area:		cancer
Launch Year/Probability:		2021/80%
2024 Sales	Morningstar	$570 million
	Consensus	$508 million
Market Model:		—

In a phase 2 prostate cancer study, the drug showed favorable trends in PSA response rates. A phase 3 study for prostate patients following a novel androgen drug should read out in 2020.

Product:		ABL001
Composition:		small molecule (BCR-ABL)
Economics:		
Therapeutic Area:		cancer CML
Launch Year/Probability		2022/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	$166 million
Market Model:		—

With only limited data, we remain skeptical this drug will develop into a blockbuster, even though that is the guidance by Novartis. Given how effective Gleevec and Tasigna are, we believe the hurdle for this drug is exceptionally high. There could be a place for the drug in the refractory CML market, but we estimate that is a very small market. In a phase 1 study, the drug showed response rates of 43-60% in refractory patients. Phase 3 data should be ready by year end 2020. Novartis plans to file the drug in third-line CML in 2021.

Product:		QGE031/ligelizumab
Composition:		Biologic (IgE)
Economics:		
Therapeutic Area:		chronic spontaneous urticaria/CIU
Launch Year/Probability		2022/70%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		—

Early data suggested a benefit of the drug over Xolair, but phase 3 data (expected in late 2021) is needed before our expectations increase to meaningful sales from the drug.

Product:		Iscalimab/CFZ533
Composition:		Biologic (anti CD40)
Economics:		
Therapeutic Area:		transplant
Launch Year/Probability:		2024/75%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		—

While very early stage data is encouraging, we need to see the phase 2 data before adding significant sales into our model. The phase 2 data in kidney transplant should be available by 2021, which Novartis expects to file on in 2023.

Product:		LNP023
Composition:		Small molecule (Factor B inhibitor)
Economics:		
Therapeutic Area:		paroxysmal nocturnal hemoglobinuria (PNH) and renal diseases
Launch Year/Probability		2024/25%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		—

LNP023 will likely target PNH as its initial indication. Early phase 2 data suggests good efficacy, but full phase 2 data (expected in 2020-2021) is needed to assess the drug's prospects. Potential phase 3 data could be ready by late 2022 followed by date in several renal disorders.

Product:		Adriforant
Composition:		Small molecule (H4 receptor antagonist)
Economics:		
Therapeutic Area:		Moderate atopic dermatitis
Launch Year/Probability		2024/25%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		atopic dermatitis (p. 164)

With reasonable data on reducing EASI (close to 50% versus placebo), the drug should start a phase 3 program in 2021 following more early stage data.

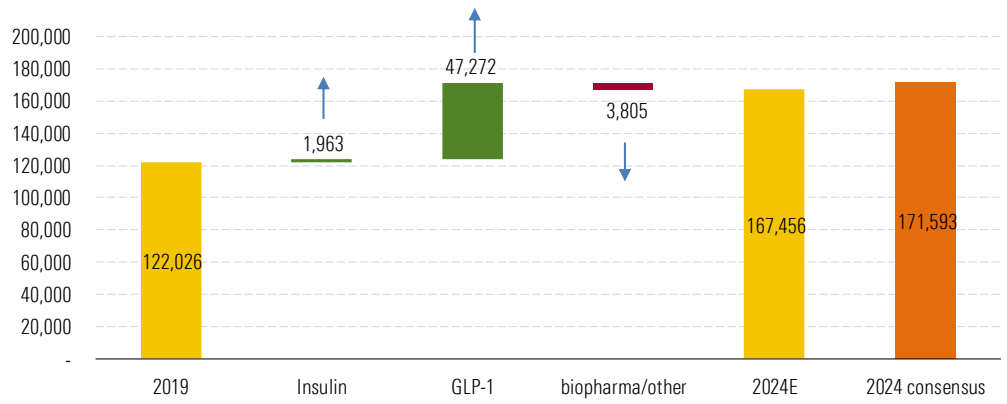
Product:		TQJ230/AKCEA-APO(a)-LRx
Composition:		Biologic (inhibiting Lp(a))
Economics:		Gained drug from Ionis and Akcea for upfront payment of $150 million
Therapeutic Area:		Cardiovascular disease
Launch Year/Probability		2025/25%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	NA
Market Model:		—

While TQJ230 showed strong phase 2b data in November 2018, the drug will likely need to show positive phase 3 outcomes data expected in 2024 before gaining approval. In a phase 2 study, the drug showed a dose dependent response rate on Lp(a) with the drug lowering the endpoint by over 50% at the 60mg monthly dose. The outcomes study is using 80mg monthly. Elevated Lp(a) has shown a causal link to cardiovascular disease.

Novo Nordisk NVO

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$62.00	1.06	Medium	Wide	Stable

Revenue Breakdown DKK Millions



Source: Morningstar, company reports; DrugAnalyst, Visible Alpha for consensus.

Next-Generation Insulin and GLP-1 Drive Sustainable Growth Despite Continued Price Headwinds

Expiring Patents

While human insulin has long been in decline, modern insulins are also beginning to see generic and biosimilar threats, but complex devices and economies of scale in manufacturing limit the number of potential competitors. Growth hormone Norditropin (2017 expiration) continues to compete well despite cheaper entrants, and hemophilia drug NovoSeven is seeing pressure from Roche's Hemlibra.

Inline Products

Novo Nordisk claims 29% of the global diabetes drug market, which is poised to continue growing at a mid-single-digit rate. As the prevalence of diabetes soars and diagnosis and treatment rates climb, we expect insulin volume growth for the foreseeable future, but pricing pressure in the U.S. (due to biosimilar entrants and Medicare-related reimbursement pressure) and GLP-1 demand (slowing insulin demand growth) counter this volume growth. Novo Nordisk's once-weekly GLP-1 Ozempic is cannibalizing its own once-daily GLP-1 Victoza but also countering pressure from Eli Lilly's once-weekly product Trulicity, and Novo Nordisk's oral GLP-1 Rybelsus opens up potential to draw new patients (currently on orals) into this class.

Pipeline

Novo Nordisk's pipeline is heavily focused on expanding the use of GLP-1 therapies beyond diabetes, particularly in obesity (potential semaglutide launch in 2022) and NASH (potential launch 2023). With concizumab's failure, hemophilia remains a weakness, as next-generation treatments in the pipeline

don't look capable of outweighing the hit from disruptive threats (Roche's Hemlibra, Alnylam's fitusiran) to the NovoSeven franchise.

Moat and Product Portfolio

Expiring Patents

Product:		human insulin	Continued switching to superior modern and next-generation insulins should lead to human insulin declines.
Composition:		biologic	
Economics:		—	
Therapeutic Area:		diabetes	
Patents/Generic Threats:		expired	
2024 Sales:	Morningstar	DKK 6.9 billion	
	Consensus	NA	
Market Model:		—	

Product:		NovoRapid/NovoLog	Novo Nordisk and Eli Lilly control the rapid-acting insulin market, which is characterized by exclusive PBM contracts and heavy discounting, as NovoRapid's similarity to Eli Lilly's Humalog makes for a competitive market. Sanofi's biosimilar Humalog, known as Admelog, received FDA approval in December 2017 and EU approval in July 2017. Sanofi launched in early 2018. Admelog is mainly competing in the lower-margin Medicaid portion of the market, but is still pressuring contract pricing in the broader commercial market. We expect it could be difficult for players beyond Sanofi (which already is a leading player in the long-acting insulin market) to gain significant share, limiting the downside for NovoLog.
Composition:		biologic (rapid-acting modern insulin)	
Economics:		—	
Therapeutic Area:		diabetes	
Patents/Generic Threats:		expired	
2024 Sales:	Morningstar	DKK 15.8 billion	
	Consensus	DKK 14.5 billion	
Market Model:		insulin (p.176)	

Product:		NovoMix	NovoMix is still growing in emerging markets like China, but Ryzodeg's launch--Novo Nordisk's new mix regimen that includes basal insulin Tresiba--should lead to steadier NovoMix declines.
Composition:		biologic (NovoRapid mix)	
Economics:		—	
Therapeutic Area:		diabetes	
Patents/Generic Threats:		expired	
2024 Sales:	Morningstar	DKK 9 billion	
	Consensus	DKK 8.6 billion	
Market Model:		insulin (p.176)	

Product:		Levemir	Levemir's U.S. basal insulin share gains and pricing power have ended. Pricing in the long-acting market has been hit first by the growing price discrepancy between Sanofi's Lantus and Levemir, and then by the introduction of biosimilar Lantus (Eli Lilly's Basaglar) at the end of 2016. We continue to assume low-single-digit pricing pressure in the U.S. long-acting market in the long run, following a more difficult 2017-18. While Merck and Samsung Bioepis have exited the biosimilar Lantus market, Mylan and Biocon's Semglee is approved in Europe and could reach the U.S. market in late 2020 (approved in June 2020 as a BLA). We expect Levemir will continue to grow in emerging markets, and U.S. volume could remain flat due to steady formulary access.
Composition:		biologic (long-acting modern insulin)	
Economics:		—	
Therapeutic Area:		diabetes	
Patents/Generic Threats:		2019 U.S./2019 EU	
2024 Sales:	Morningstar	DKK 5.2 billion	
	Consensus	DKK 5.2 billion	
Market Model:		insulin (p.176)	

Product:		NovoSeven
Composition:		biologic (recombinant protein)
Economics:		—
Therapeutic Area:		hemophilia
Patents/Generic Threats:		expired
2024 Sales:	Morningstar	DKK 6.1 billion
	Consensus	DKK 5.6 billion
Market Model:		hemophilia (p.173)

NovoSeven has carved out a niche as an expensive treatment for hemophilia patients with inhibitors. Manufacturing challenges and Novo Nordisk's brand will protect NovoSeven from biosimilar competition in developed markets, but branded competition is now affecting NovoSeven's sales. Shire's Feiba gained a label for prophylaxis of bleeds (versus NovoSeven's on-demand use), which led to increased growth for Feiba and slightly less demand for NovoSeven. In addition, Roche's Hemlibra was approved in November 2017 in the U.S. as a prophylaxis therapy for inhibitor patients and only needs to be taken once weekly or even once monthly subcutaneously, versus Feiba's every-two-day infusion. We expect NovoSeven to see declines over the next several years but that patient demand for treatment of bleeds (not prophylaxis) will allow the drug to maintain close to half of its peak 2015 sales of DKK 10 billion in 2022.

Product:		Norditropin
Composition:		biologic (recombinant protein)
Economics:		—
Therapeutic Area:		growth-related disorders
Patents/Generic Threats:		expired
2024 Sales:	Morningstar	DKK 6.3 billion
	Consensus	DKK 8 billion (includes DKK 1.7 billion somapacitan)
Market Model:		—

Norditropin is the only liquid room-temperature-stable human growth hormone in a prefilled device. Pricing headwinds hit Norditropin in the U.S. in 2017, as competitors grew more aggressive on price and Norditropin was excluded from a large formulary. Novo Nordisk's once-weekly product somapacitan could help differentiate from competition, but we do not yet explicitly model sales, as we're waiting for evidence that efficacy in children (50% of the market opportunity) at least matches that of Norditropin. So far, Novo Nordisk has presented positive phase 3 data in adults (to be approved here in the second half of 2020) and phase 2 data in children (phase 3 results H2 2021E). Other long-acting growth hormone products from Pfizer/Opko (hGH-CTP) and Versartis (somavaratan) failed to achieve similar efficacy to Genotropin, but Ascendis' TransCon once-weekly product showed superior annualized height velocity versus Genotropin in a phase 3 pediatric growth hormone deficiency study in March 2019, and FDA filing is expected in Q2 2020E (starting phase 3 in adult GHD in 2020).

Inline Products

Product:		Tresiba
Composition:		biologic (ultra-long-acting modern insulin)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2029 U.S./2028 EU
2024 Sales:	Morningstar	DKK 12.1 billion
	Consensus	DKK 11.7 billion
Market Model:		insulin (p.176)

While Tresiba is gaining volume share, it faces a tough pricing environment and lower market volume growth due to the success of GLP-1 therapies, and we continue to assume low-single-digit pricing pressure in the U.S. long-acting market in the long run, following a more difficult 2017-18. Sanofi's Toujeo and Novo Nordisk's Tresiba are recently launched next-generation products that are meant to improve the safety and convenience of long-acting insulin, reducing the risk of overall hypoglycemia and nocturnal hypoglycemia and offering more flexible dose timing. Tresiba's U.S. launch coincided with the entry of Basaglar (biosimilar Lantus), reducing Novo Nordisk's ability to see a price premium. Novo Nordisk's next-generation drug gained commercial coverage in 2017 and 2018, and Sanofi's Medicare Part D exclusions beginning in 2018 allowed Novo Nordisk to gain share, although it has to compete with Basaglar and likely will continue to compete on price. Hypoglycemia data from the Switch studies and Devote was strong and should boost access, as data was added to the U.S. prescribing label in March 2018 (a hypoglycemia benefit versus Lantus was added to the label in Europe in 2017).

Product:		Victoza
Composition:		biologic (GLP-1 hormone)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2024 U.S./2022 EU
2024 Sales:	Morningstar	DKK 8.3 billion
	Consensus	DKK 7.7 billion
Market Model:		noninsulin diabetes (p.175)

Victoza's dominance in the GLP-1 market is fading, as the once-daily treatment now competes with once-weekly products Trulicity (from Eli Lilly) and Ozempic (from Novo Nordisk). Victoza was famously excluded from Express Scripts' national formulary in 2014, but patients were grandfathered in on Victoza treatment by gaining medical exemptions, and physicians successfully argued for the drug's differentiation from older therapies Byetta and Bydureon. Strong cardiovascular outcomes data for Victoza led to a prescribing label update in the U.S. in August 2017 for patients with type 2 diabetes and CV disease, following similar label updates for Victoza and Saxenda in Europe. The Leader study showed that Victoza lowered the risk of a composite endpoint of cardiovascular death, heart attack, and stroke by 13% versus placebo, with cardiovascular death risk lowered by 22%. However, positive cardiovascular outcomes for competing oral SGLT2 therapy Jardiance creates tension between these two classes. Victoza's inclusion on China's national drug reimbursement list in August 2017 should expand access and accelerate Victoza's ex-U.S. growth despite competition.

Product:		Ozempic (once-weekly injectable semaglutide)
Composition:		biologic (GLP-1 hormone)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2031 U.S./EU
2024 Sales:	Morningstar	DKK 40 billion
	Consensus	DKK 38.4 billion
Market Model:		noninsulin diabetes (p.175)

Once-weekly semaglutide extends Novo Nordisk's GLP-1 sales, allowing Novo Nordisk to compete with Eli Lilly's once-weekly Trulicity and defend against Victoza generics; the drug received FDA approval in December 2017. Novo Nordisk's SUSTAIN trials for Ozempic generally showed A1C lowering around 1.5% and weight loss of 5-6 kg, and the SUSTAIN 7 trial specifically showed superiority on both of these measures to Eli Lilly's Trulicity. That said, both firms are battling for improvements with high-dose versions; the highest 4.5 mg dose of Trulicity showed 1.9% A1C lowering and weight loss of 4.7 kg in the Award-11 study in May 2020 (likely to see expanded approval later in 2020), and Novo Nordisk should see data from the high-dose Ozempic trial Sustain Forte, testing 1 mg versus 2 mg doses, in Q4 2020. We're also encouraged by the October 2018 ADA guidelines that give GLP-1 therapies like Victoza and Ozempic strong positioning, recommended as first injectables (ahead of insulin) and in many patients as a preferred second treatment option, after generic metformin. Overall, we expect Novo Nordisk's GLP-1 franchise to continue to dominate with more than 50% of the global market for the foreseeable future (and we see the GLP-1 market growing from $10 billion in 2019 to more than $15 billion by 2024). Ozempic showed a 26% reduced risk of major adverse cardiovascular events (Mace) in the Sustain-6 CV outcomes trial, and Novo Nordisk received clearance for this CV benefit on its prescribing label in January 2020. While not head-to-head, these results look better than Eli Lilly's once-weekly GLP-1 Trulicity, which saw a 12% reduction in Mace in the Rewind trial (21% among high-risk patients, which could be a truer comparison to Sustain-6). Eli Lilly obtained a broader CV benefit label than Ozempic in Feb 2020, but we think Ozempic's edge in high-risk patients and better blood sugar and weight loss data still give it a slight edge over Eli Lilly. Novo Nordisk is also testing Ozempic's effect on diabetes-related complications like diabetic eye disease (Focus trial, data 2025E) and kidney disease (Flow trial, data 2024E). We still see new competitive threats from Eli Lilly; novel GIP/GLP-1 tirzepatide (head-to-head data against Ozempic in 2021E, launch 2022E). Eli Lilly's GIP-GLP-1 data (A1C reductions of 1.6%-2.4% and weight loss of 4.8-11.3 kg at a range of doses) surpassed Trulicity's efficacy (1.1% A1C reduction and 2.7 kg weight loss) in the study, but also showed the potential to surpass Ozempic. Novo Nordisk began a phase 1 trial of a once-weekly GIP in combination with Ozempic, to isolate the best dosing combination in first-quarter 2020.

Product:		Ryzodeg
Composition:		biologic (NovoRapid + Tresiba)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2029 U.S./2028 EU
2024 Sales:	Morningstar	DKK 1.7 billion
	Consensus	DKK 2.3 billion
Market Model:		insulin (p.176)

Ryzodeg's better blood sugar control than NovoMix should allow it to extend Novo Nordisk's insulin mix sales, but due to a declining market in the U.S. for such therapies, launches should largely be focused outside the U.S. (including Japan, Mexico, India, and the Middle East).

Product:		Xultophy
Composition:		biologic (Tresiba + Victoza)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2029 U.S./2028 EU
2024 Sales:	Morningstar	DKK 4.4 billion
	Consensus	DKK 4.8 billion
Market Model:		insulin (p.176)

A fixed-ratio combination of Tresiba and Victoza offers stronger efficacy and reduced side effects compared with either drug alone, but the drug is off to a slow start, as it is not approved in the U.S. as a first-line injectable. Sanofi's Soliqua (Lantus and GLP-1 therapy Adlyxin) and Xultophy were both approved in November 2016. Compelling data on hypoglycemia risk reduction and weight loss from Xultophy's Dual VII study (89% reduction in rate of severe or blood glucose confirmed symptomatic hypoglycemia and weight loss of 0.9 kg instead of a 2.6 kg weight gain, versus Lantus and rapid-acting insulin combo) could support steady pricing and help differentiate from Soliqua (Sanofi's GLP-1 did not see a cardiovascular benefit, so the drug is widely believed to be less effective than Victoza). However, Xultophy (and Victoza) do have a black-box warning for thyroid cell tumor risk (seen in rodents), something that Sanofi's label lacks.

Product:		Saxenda
Composition:		biologic (GLP-1 hormone)
Economics:		—
Therapeutic Area:		obesity
Patents/Generic Threats:		2024 U.S./EU
2024 Sales:	Morningstar	DKK 4.8 billion
	Consensus	DKK 7.3 billion
Market Model:		—

Approved by the FDA in late 2014, 3 mg liraglutide faces an uphill battle in winning over physicians, patients, and payers wary of obesity drug side effects. However, the drug is now launching globally and seeing strong growth. Saxenda leads the U.S. market in value share and is gaining share over other medications (Contrave, Belviq, Qsymia). While the obesity market is huge--650 million globally and only 2% treated--Novo Nordisk is targeting patients with comorbidities and BMI above 35. Semaglutide is now positioned as a next-generation obesity treatment (likely launch in 2022), and several phase 1 programs could prove complementary to GLP-1 therapy.

Product:		Fiasp (Faster-acting insulin aspart, NN1218)
Composition:		biologic (ultra-rapid modern insulin)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2030 U.S./EU (formulation)
2024 Sales:	Morningstar	DKK 2.7 billion
	Consensus	DKK 3.6 billion
Market Model:		insulin (p.176)

Fiasp produced data showing noninferiority to NovoRapid in early 2015, and despite a complete response letter from the FDA in October 2016 regarding an assay used for immunogenicity and pharmacology data, it launched in the U.S. in fourth quarter 2017. Fiasp acts more rapidly than NovoRapid, which could make it a more appealing option for patients requiring higher doses of insulin (type 1 diabetes patients account for fewer than 10% of diabetes patients, but 10%-20% of insulin use). However, without significant differentiation from NovoRapid, we think Fiasp's potential could be limited by rapid-acting insulin biosimilars, and Sanofi's Admelog launched in the U.S. and Europe in 2018. This could push Novo Nordisk's rapid-acting insulin growth below insulin volume (demand) growth. That said, rapid-acting insulin pricing is already quite low, and cost advantages would probably keep all but a handful of current insulin players from gaining substantial share.

Product:		Rebinyn/Refixia (N9-GP)
Composition:		biologic (recombinant protein)
Economics:		—
Therapeutic Area:		hemophilia B
Patents/Generic Threats:		2028 U.S./2027 EU (est)
2024 Sales:	Morningstar	DKK 1.1 billion
	Consensus	DKK 1.1 billion
Market Model:		hemophilia (p.173)

Novo Nordisk has pointed to Refixia's long half-life as a benefit over Bioverativ/Sobi's Alprolix, but we think Refixia is at a disadvantage in the long-acting factor IX market. Both Alprolix and CSL's Idelvion were approved ahead of Refixia, and both allow every two-week dosing for prophylaxis. Refixia was approved as a weekly product in Europe in 2017, and its approval in the U.S. (as Rebinyn) did not contain an indication for prophylaxis (only on-demand use). In addition, all the long-acting factor IX products are potentially vulnerable to Sanofi/Alnylam's disruptive therapy fitusiran (phase 3 data expected in the first half of 2021) or potential gene therapy (Spark/Pfizer and Uniqure both in phase 3).

Product:		Esperoct/N8-GP/NN7088 & NovoEight
Composition:		biologic (recombinant protein)
Economics:		—
Therapeutic Area:		hemophilia A
Patents/Generic Threats:		N8-GP: 2019 (80%)
2024 Sales:	Morningstar	DKK 1.8 billion
	Consensus	DKK 3.2 billion
Market Model:		hemophilia (p.173)

NovoEight launched in the U.S. in 2015 and gained some traction on formularies as a me-too Advate. Esperoct's four-day to potentially weekly dosing schedule puts it on par with other long-acting products, but manufacturing delays pushed filing to first quarter 2018 in U.S./EU; it was approved in the U.S. in Feb 2019, and is launching in 2020 (due to IP issues), well behind the options from Sanofi/Sobi, Takeda, and CSL. A daily subcutaneous version of Esperoct also entered phase 1 in 2017, which could have offered improved convenience over infusions, but the program was discontinued in November 2018 due to anti-drug antibodies. With Roche's Hemlibra launching as a once-weekly or once-monthly subcu injection, and Alnylam's fitusiran potentially launching in 2022 as a once-monthly injection, we don't anticipate much demand.

Product:		Rybelsus (oral semaglutide)
Composition:		biologic (GLP-1 hormone)
Economics:		low-single-digit royalty to Emisphere, co-promote with Merck in Japan
Therapeutic Area:		diabetes
Patents/Generic Threats:		2031 (tablet 2034)
2024 Sales:	Morningstar	DKK 25.5 billion
	Consensus	DKK 28.2 billion
Market Model:		noninsulin diabetes (p.175)

Novo Nordisk's oral GLP-1 Rybelsus received FDA approval in Sept 2019, European approval in April 2020, and Japan approval in June 2020, giving Novo Nordisk the ability to draw diabetes patients away from other oral regimens earlier than it could with injectable GLP-1 and insulin therapies. We think peak sales will surpass $3 billion as Novo Nordisk expands into the oral diabetes therapy market, and while list price is similar to that of Ozempic and other injectables, we expect net Rybelsus pricing will fall over time to roughly $2,500 in the U.S., which would be a slight premium to net prices of other orals (we assume around $2,000) but a clear discount to Novo Nordisk's current injectable GLP-1 therapies, Victoza and Ozempic (we assume $4,000). The drug has shown slightly lower efficacy than Ozempic (3-5 kilograms of weight loss and 1.1-1.5% A1C reductions) but proved superior to both Victoza and Trulicity (at the highest 14 mg dose tested in Pioneer 4 and Pioneer 10) on both of these measures. In the Pioneer-6 CV study, the 14 mg dose was noninferior on MACE (21% reduction, not statistically significant), but the reduction in risk of CV death (HR 0.49), and all-cause mortality (HR=0.51) were significant and impressive for a relatively small, short study. Novo Nordisk started a larger CV outcomes study, Soul, in the second quarter of 2019, which should produce data by 2024. Oral administration requires Novo Nordisk to use a much higher (14 mg per day) dose than for Ozempic (1 mg weekly), but we expect margins for Rybelsus to become similar to Novo Nordisk's firmwide margins with time (particularly as the firm is making progress with improved formulations). Eli Lilly has a potential oral GLP-1 competitor, but it is just entering phase 1. We expect Rybelsus to perform strongly even if Eli Lilly's GIP/GLP-1 launches in 2023, as the oral market gives Novo Nordisk greater access to primary care physicians as well as an opportunity to offer a slightly discounted price, and the drug should have a three-year lead in the race to the market.

Moat Trend and Product Pipeline

Product:		Injectable semaglutide
Composition:		biologic (GLP-1 hormone)
Economics:		—
Therapeutic Area:		obesity
Launch Year/Probability:		2022 (80%)
2024 Sales:	Morningstar	DKK 5.1 billion
	Consensus	DKK 5.2 billion
Market Model:		—

Novo Nordisk improves on Saxenda's efficacy with once-weekly 2.4 mg semaglutide, confirmed by phase 3 data from the STEP program. In STEP 4 data released in May 2020, overweight or obese patients taking semaglutide for 68 weeks saw 17.4% weight loss, while those taking the drug for 20 weeks followed by 48 weeks of placebo lost some weight and then regained most of the weight. In key trial Step 1 in June 2020, semaglutide also led to a roughly 15% weight loss versus 2.4% on placebo. Novo Nordisk saw smaller benefits, as expected, in 68-week trials among diabetics (STEP 2: 9.6% weight loss, 2.4 mg, versus 3.4% placebo) and obese patients on diet and exercise programs (STEP 3: 16% weight loss versus 5.7% placebo) in June 2020. Head-to-head data against liraglutide (Saxenda) should be available from STEP 8 in 2021. In phase 2, semaglutide showed 16.2% weight loss over one year at the highest dose and a solid safety profile. Beyond semaglutide, Novo Nordisk's amylin analog AM833 appeared to have strong efficacy in phase 1 (patients had 3.5% lower body weight versus placebo at the 30 ug/kg dose after one month), and additional data in June 2020 were also encouraging (phase 2 monotherapy data showed 10.8% weight loss at 4.5mg weekly dose versus 3% placebo after 26 weeks, and phase 1 combination data with semaglutide showed 17% weight loss without additional side effects after 20 weeks of treatment). The combination approach could allow Novo Nordisk to hit 25% weight loss with longer-term data, closer to the level of bariatric surgery. Novo Nordisk is also testing potential combinations of semaglutide with phase 1 PYY-targeting therapies and has a GLP-1/glucagon co-agonist and GLP-1/glucagon/GIP tri-agonist in phase 1, as well (data expected H1 2020). Eli Lilly has also moved its GIP-GLP-1 tirzepatide into phase 3 in obesity (data 2022E). Independently run mid-stage studies of liraglutide in Alzheimer's will be reading out in 2020, and if positive, Novo Nordisk could advance semaglutide (which is more brain permeable) in this indication and vascular dementia, but we do not incorporate sales into our Novo Nordisk model.

Product:		Injectable semaglutide
Composition:		biologic (GLP-1 hormone)
Economics:		—
Therapeutic Area:		NASH
Launch Year/Probability:		2023 (60%)
2024 Sales:	Morningstar	DKK 2.6 billion
	Consensus	NA
Market Model:		—

Novo Nordisk is pursuing semaglutide in NASH, a disease that affects 33 million patients in the U.S. and Europe but lacks approved treatments. We assume a 60% probability of a 2023 launch. In May 2020, three once-daily doses (0.1mg, 0.2mg, 0.4mg) in a phase 2 study met the primary endpoint (resolution of NASH, no worsening of liver fibrosis) versus placebo, and at the highest dose, NASH resolution was 59% (versus 17% for patients on placebo). While there was no statistically significant benefit on fibrosis improvement, there appears to have been a trend to improvement, and with a strong safety profile, we expect Novo Nordisk to move forward to phase 3. Based on Victoza's midstage NASH data, we expected semaglutide could have key role in treatment, but subcutaneous dosing could be cumbersome relative to many oral pipeline alternatives. Novo Nordisk also moved into a phase 2 combination study as part of a collaboration with Gilead, and once-weekly subcutaneous injections in this trial (along with daily pills FXR agonist cilofexor and ACC inhibitor firsocostat) seem more convenient (data expected third-quarter 2020). Novo Nordisk's strong endocrinologist-focused salesforce could complement Gilead's own hepatologist-focused salesforce in NASH. Eli Lilly also moved its GIP/GLP-1 drug tirzepatide into a phase 2 study in NASH as a once-weekly subcutaneous regimen, with data expected in 2022. Novo Nordisk's NASH pipeline could eventually include its amylin analog AM833 (in phase 2 in obesity), PCSK9 peptide therapy (in phase 1 for cholesterol-lowering), UD-014 (preclinical drug licensed from UBE), or a drug from a collaboration with Dicerna (RNAi).

Product:		concizumab
Composition:		biologic (TFPI antibody)
Economics:		—
Therapeutic Area:		hemophilia
Launch Year/Probability:		2022/0%
2024 Sales:	Morningstar	—
	Consensus	DKK 900 million
Market Model:		hemophilia (p. 173)

A first-in-class tissue factor pathway inhibitor, concizumab was on track to produce phase 3 data from two trials in H1 2021, trials were paused in March 2020 due to nonfatal thrombotic events in three patients. Because of the drug's upstream targeting, it is targeted to hemophilia A and B, including patients with inhibitors. While dosing is subcutaneous (more convenient than older IV treatments), once-daily administration does not look as convenient as once-monthly dosing for Roche's Hemlibra (approved for hemophilia A patients). Phase 2 Explorer 4 and 5 studies provided positive safety and efficacy data. The closest competition would be from Pfizer's TFPI therapy marstacimab, which entered phase 3 in early 2020. Bayer's BAY1093884 also targets TFPI but is still in phase 1. Novo Nordisk also has Mim8 (a Genmab-partnered bispecific antibody that could be similar to Hemlibra and entered phase 1/phase 2 in first-quarter 2020) as well as a research-stage collaboration with Bluebird bio for an integrating hemophilia A gene therapy (which could serve pediatric indications), but neither of these are in our valuation model, either.

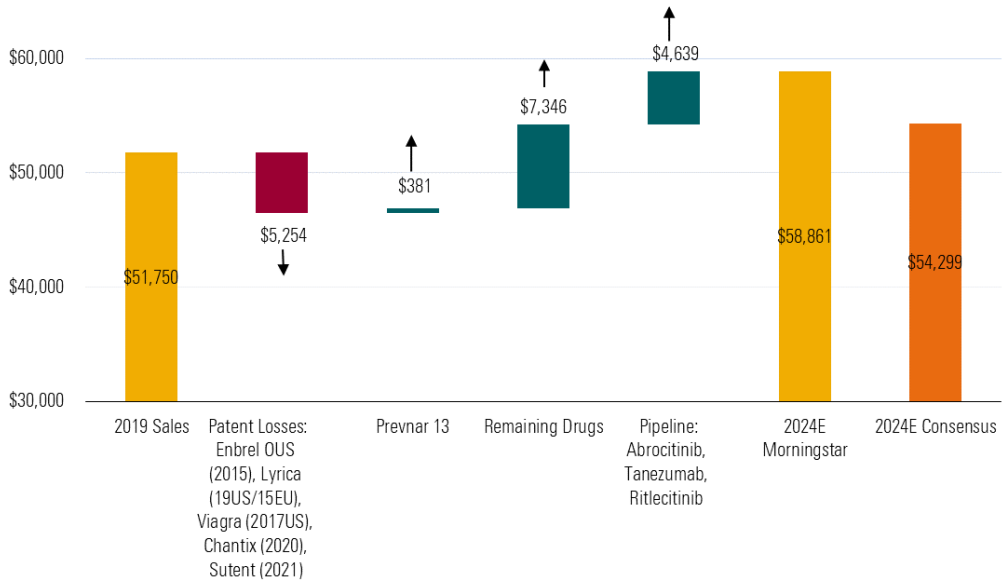
Product:		LAI287 (insulin icodec)
Composition:		biologic (long-acting basal insulin)
Economics:		—
Therapeutic Area:		diabetes
Launch Year/Probability:		2023/60%
2024 Sales:	Morningstar	DKK 1.8 billion
	Consensus	—
Market Model:		insulin (p. 176)

Novo Nordisk reported positive phase 2 data for once-weekly basal insulin LAI287 in February 2020 and is moving into phase 3 development in fourth-quarter 2020. If approved, LAI287 would offer patients a more convenient regimen that could improve compliance and outcomes, but efficacy benefit so far is unclear. In phase 2, LAI287 proved non-inferior to Lantus on blood glucose lowering (1.33% reduction for icodec and 1.15% for Lantus), with similar rates of hypoglycemia. The drug's enhanced albumin binding gives it a longer half-life in the body. The program could be key to allowing Novo Nordisk to gain more share in the long-acting insulin space, which continues to be under pricing pressure from biosimilars; Mylan's Semglee was approved as a new biologic in June 2020. Novo Nordisk is also working on a combination of LAI287 and semaglutide, or icosema, and has completed phase 1 of development.

Pfizer PFE

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★★	$42.50	0.81	Low	Wide	Stable

Revenue Breakdown USD Millions



Source: Morningstar, company reports; DrugAnalyst/S&P Cap IQ for consensus.

Inline Product Strength of Ibrance and Immunology Pipeline is Key

Expiring Patents

Pfizer faces moderate patent losses with Lyrica (2019-20 U.S.), Chantix (2020-21), Sutent (2021), and some declines for international Enbrel sales (2015, but a biologic).

Inline Products

Growing cancer drug Ibrance and cardiomyopathy drug Vyndaqel internationally are important for inline product growth, as are global sales for oncology drugs Xtandi, Braftovi, and Mektovi.

Pipeline

The immunology drug abrocitinib and pain drug tanezumab hold new mechanisms of action in areas of unmet medical need that look underappreciated.

Moat and Product Portfolio

Expiring Patents

Product:		Lyrica
Composition:		small molecule (GABA)
Economics:		mid-single-digit royalty
Therapeutic Area:		fibromyalgia, neuropathic pain
Patents/Generic Threats:		June 2019 U.S./2014-22 international
2024 Sales	Morningstar	$757 million
	Consensus	$752 million
Market Model:		—

With the patent loss in most major markets already happened, the once highly successful Lyrica is fading quickly due to generic competition, and we don't expect this drug to be a major driver for the company in developed markets. However, the drug should have some staying power in emerging markets where brand strength can be more powerful than patents.

Product:		Enbrel
Composition:		biologic (anti-TNF)
Economics:		1% royalty, PFE hold rights outside U.S./Canada
Therapeutic Area:		immunology
Patents/Generic Threats:		2015 international
2024 Sales	Morningstar	$710 million
	Consensus	$790 million
Market Model:		psoriasis (p.166), RA (p.167)

Increasing competition from superior branded drugs (IL-17s and IL23s) along with biosimilar pressures will likely drive continued declines. Biosimilars from Biogen/Samsung (Benepali, EU approval in 2016) and Novartis (Erelzi, EU approval in June 2017) will likely take more share but at a slower pace than a traditional small-molecule generic due to the complexities of the biologic structure of Enbrel. Mylan will likely enter the European market with a biosimilar version of Enbrel as well. Pfizer also has a biosimilar version of Enbrel, which should give Pfizer increased options.

Inline Products

Product:		Prevnar 13
Composition:		vaccine
Economics:		—
Therapeutic Area:		streptococcus pneumoniae
Patents/Generic Threats:		2026 U.S./international, 2029 Japan
2024 Sales	Morningstar	$6,228 million
	Consensus	$6,210 million
Market Model:		—

Prevnar 13 should continue to dominate the pneumococcal market, but a competitive threat from Merck's 15-valent V114 is in phase 3 development. The wider range of coverage from Merck's vaccine could threaten Prevnar 13, but one phase 2 study didn't support similar efficacy as Prevnar in infants.

As background Merck's vaccine would cover the same valents as Prevnar 13, but would add 22f and 33f, which would cover 15% more cases of the disease. However, Pfizer's 20-valent covers all the valents in Prevnar 13, the two additional valents in the Merck vaccine and 8, 10a, 11a, 12f, 15b, which covers 15% more cases than the new Merck vaccine.

Pfizer should file its 20 valent vaccine for adults in late 2020 following strong phase 3 data. The first of three key phase 3 studies (reported in March 2020) showed similar protection against all the valents from Prevnar 13 and 6 of the 7 additional valents with one valent trending well. The phase 3 data compared against Pneumovax23 (from Merck) which isn't conjugated and not good for infants. The second phase 3 study (reported in May 2020) showed good safety across production lots. We expect Pfizer to file the vaccine following the last phase 3 study in adults.

Based on strong phase 2 data, Pfizer started its phase 3 study in infants in June 2020 with the 20-valent vaccine. With close to 70% of Prevnar 13 revenue from infants, this data will be important. Merck should have the majority of its phase 3 data in adults and infants in 2020, which may give Merck a minor lead in infants. Merck recently began highlighting V116, which should cover more valents than V114, but Merck hasn't disclosed details for this vaccine.

Product:		Ibrance
Composition:		small molecule (CDK 4/6)
Economics:		8% royalties to Amgen
Therapeutic Area:		breast cancer
Patents/Generic Threats:		2028 U.S./EU
2024 Sales	Morningstar	$7,164 million
	Consensus	$8,767 million (before Pallas announcement)
Market Model:		non-HER2+ breast cancer (p.183)

Ibrance's first-mover advantage in metastatic breast cancer along with no significant efficacy advantage coming from Novartis' and Eli Lilly's CDK 4/6 drugs should drive Ibrance's market share close to 75% in the metastatic disease setting. Pfizer's Ibrance gained approval with over a two-year head start in the U.S. and close to a one-year early-mover advantage in Europe. As of late 2018, CDK 4/6 drugs had penetrated 64% of the U.S. market and Ibrance had 91% share. In Europe as of April 2020, the drug had 68% market share of the CDK4/6 market, but the CDK4/6 market only had 38% of the market so there is room for growth in Europe in particular even though some pricing contracts might lead to lower prices and some volatility. While the adjuvant study Penelope (high risk patients) should report in late 2020, the adjuvant study Pallas reported no benefit in May 2020. The Patina study in the HER2+ breast cancer patient group (in combination with Herceptin or Perjeta) should report in late 2021.

Product:		Xeljanz
Composition:		small molecule (JAK)
Economics:		—
Therapeutic Area:		immunology
Patents/Generic Threats:		2025 U.S./2027 EU/2025 Japan
2024 Sales	Morningstar	$3,487 million
	Consensus	$3,100 million
Market Model:		RA (p.167), Crohn's/UC (p.168)

Xeljanz has moved up the treatment guidelines for rheumatoid arthritis and gained approval in Europe in 2017, which should support the strong growth rate. American College of Rheumatology guidelines have evolved, pushing new treatment options continually up the treatment cascade. Over the last three major updates from ACR (in 2008, 2012, and 2015), biologics and new treatments continue to move further up the recommended treatment pathway. Also, the 2018 approval in ulcerative colitis (UC) should further drive growth. The drug is in a phase 3 study for ankylosing spondylitis, which should complete in 2020. However, the mid-2019 FDA update limiting the 10mg twice daily dosage due to blood clots and death as well as moving the UC indication to second line is concerning, but the drug's strong efficacy data was seen at lower doses as well.

Product:		Eliquis
Composition:		small molecule (Factor Xa)
Economics:		~40% of profits to Bristol
Therapeutic Area:		cardiovascular/AFib
Patents/Generic Threats:		2026 global
2024 Sales	Morningstar	$6,555 million
	Consensus	$6,536 million
Market Model:		atrial fibrillation (p.172)

Eliquis' superior data on stroke prevention, low bleeding rates, and mortality should drive leading share in atrial fibrillation and offset its late market entry. PFE/BMY's Eliquis should net 50%+ share in the $20 billion-plus market (up from 45% currently, twice-daily dosing, but with mortality benefit) versus Xarelto's once-daily dosing/first-mover advantage in AF, DVT/PE, and ACS (EU), which should net 30%+ share up from 25% currently at the expense of warfarin (20% market share currently). However, with no major studies ongoing for further Eliquis label expansion, we don't expect any acceleration in the drug's sales ramp.

Product:		Bavencio
Composition:		biologic (PD-L1)
Economics:		50/50 profit split with Merck KGaA
Therapeutic Area:		cancer
Patents/Generic Threats:		2033 U.S./2032 international
2024 Sales	Morningstar	$741 million
	Consensus	$526 million
Market Model:		immuno-oncology (p.181)

While Bavencio (a PD-L1 inhibitor) joined the PD-1/PD-L1 group late (approved in March 2017 for bladder cancer), the market is large enough that a smaller slice will result in meaningful sales to Pfizer. We expect global sales of Bavencio to reach $1.4 billion by 2024. While we expect Pfizer to remain at the end of the pack within this important market due to late entry without a significantly differentiated drug, we expect Bavencio to gain 3% of a $55 billion market by 2024. The drug looks best positioned in first-line renal cancer (approved in the U.S. in May 2019 and Europe in October 2019), as launch timing is closer to the leaders and a combination with Pfizer's Inlyta could help gain market share. Also, the strong data in first line bladder cancer (OS HR 0.69 at ASCO 2020) looks better than other IO drugs that have yet to show a survival benefit in this setting (approved in June 2020). A wild card is the Javelin 100 study in first-line non-small-cell lung cancer due in mid-2020, but the failure of the drug in second-line lung cancer doesn't bode well for this indication.

Product:		Steglatro/Ertugliflozin Steglujan/Ertugliflozin+Januvia
Composition:		small molecule (SGLT2)
Economics:		60% of profits to Merck
Therapeutic Area:		diabetes
Launch Year/Probability:		2031 U.S.
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$344 million
Market Model:		noninsulin diabetes (p.175)

Despite ertugliflozin's late entry into the SGLT-2 market, the development partnership with Pfizer (60% of profits to Merck/40% to Pfizer) should facilitate a fixed-dosed combination with Merck's market leading DPPIV drug Januvia. With the majority of the DPPIV market controlled by Januvia, we expect the combination of Januvia and ertugliflozin to drive market share gains despite entering the market following three established players. However, in the outcomes study (VERTIS), the drug was only non-inferior to placebo not better, which likely means the drug will have a hard time versus other SGLT2 drugs that showed a cardiovascular benefit.

Product:		Xtandi
Composition:		small molecule (antiandrogen)
Economics:		just U.S. rights (Astellas has OUS rights)
Therapeutic Area:		prostate cancer
Patents/Generic Threats:		2027 U.S.
2024 Sales	Morningstar	$1,260 million
	Consensus	$1,638 million
Market Model:		—

The lack of a need for steroids (like J&J's Zytiga) puts Xtandi in a better position. The positive phase 3 data (prosper) in nonmetastatic prostate cancer looks very similar to J&J's next-generation drug Erleada. The Arches study in metastatic hormone sensitive prostate cancer reported positive top-line data in December 2018 (opening a smaller patient set of close to 12,000 patients in the U.S.) and was approved by the FDA in December 2019. The Embark study in high-risk nonmetastatic prostate cancer should complete in mid-2020, opening up an additional 30,000 patients in the U.S.

Product:		Vizimpro/Dacomitinib
Composition:		small molecule (kinase of EGFR)
Economics:		
Therapeutic Area:		cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	$263 million
	Consensus	$339 million
Market Model:		—

The FDA approved the drug in September 2018 (followed by Europe in April 2019), but the late entry relative to Astra's Tagrisso will hurt the drug's potential. Also, the drug's efficacy and side effect profile doesn't look as good as Tagrisso.

Product:		Daurismo/Glasdegib
Composition:		small molecule (hedgehog)
Economics:		
Therapeutic Area:		cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$347 million
Market Model:		—

The FDA approved the drug in November 2018 based on excellent phase 2 data showing a 54% reduction in death in newly diagnosed acute myeloid leukemia (AML) patients. European regulators approved the drug in June 2020. However, Roche/AbbVie's Venclexta was approved the same day in the same indication, creating a competitive market. Important phase 3 data for Daurismo should report out in late 2020 in AML. While AML is a rare disease with only about 20,000 new cases annually, the five-year survival rate is only 29% (Seer data). With pricing at $200,000 a year, the drug could still be a blockbuster.

Product:		Lorbrena/Lorlatinib
Composition:		small molecule (ALK)
Economics:		20% of profits to Merck KGaA
Therapeutic Area:		cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$361 million
Market Model:		—

Lorlatinib is a potent ATP-competitive inhibitor that inhibits both ALK and ROS1 tyrosine kinase and received a breakthrough therapy designation from the FDA for ALK-positive NSCLC patients previously treated with one or more ALK inhibitors based on phase 2 data. Pfizer has shown intracranial activity and tumor responses with patients who have brain metastases, regardless of prior therapy. The FDA approved the drug in November 2018 for second-line use, followed by European approval in May 2019. A first-line study should report in late 2020.

Product:		Talzenna/Talazoparib
Composition:		small molecule (PARP)
Economics:		mid-single-digit royalties
Therapeutic Area:		cancer
Patents/Generic Threats:		
2024 Sales	Morningstar	$402 million
	Consensus	$424 million
Market Model:		—

There are currently three other PARP inhibitor drugs approved for marketing: AstraZeneca's Lynparza (olaparib), Clovis Oncology's Rubraca (rucaparib), and GSK/Tesaro Inc.'s Zejula (niraparib). While preclinical potency may not necessarily translate into clinical efficacy, Pfizer's talazoparib was seen as 100 times more potent at trapping PARP-DNA complexes than competitors such as rucaparib and olaparib, demonstrating the quality of the product. The FDA approved the drug for BRCA mutation breast cancer in October 2018 (followed by Europe in June 2019) based on the Embraca study that had a hazard ratio of 0.54 on PFS, which was like Lynparza. Also, a phase 3 study in prostate cancer in combination with Xtandi should complete in mid-2022.

Product:		Vyndaqel/Tafamidis
Composition:		small molecule (TTR attachment)
Economics:		
Therapeutic Area:		cardiomyopathy (CM)
Patents/Generic Threats:		2029 U.S. (assumes patent extension)/2026 International
2024 Sales	Morningstar	$2,179 million
	Consensus	$2,760 million
Market Model:		—

Tafamidis showed a survival benefit hazard ratio of 0.70 in the rare disease of cardiomyopathy (CM), which supported approval in May 2019 (U.S.) and February 2020 (Europe). While there is some competition in the hereditary CM space, the majority of the CM space is wild type (more than 90%). There are close to 500,000 people with CM in developed markets, but only 1% are diagnosed. Pricing is $225,000 on an annual basis in the U.S.

Product:		Braftovi/Mektovi
Composition:		small molecules (targeting BRAF and MEK mutations)
Economics:		Gained U.S. rights (and European royalty of 20-35% from Pierre Fabre and Japanese royalty of 22-25% from Ono) from through the acquisition of Array for $11.4 billion
Therapeutic Area:		Cancer
Patents/Generic Threats:		2031 U.S.
2024 Sales	Morningstar	$1,876 million
	Consensus	$1,345 million
Market Model:		—

The combination of Braftovi and Mektovi have shown excellent data in melanoma, slightly better than competitive data from Novartis and Roche with similar drugs. More important that melanoma is the first mover advantage the combination treatment has in colorectal cancer(10-15% of colorectal cancers have a BRAF mutation), where the treatment was approved by the FDA in April 2020 based on the phase 3 Beacon study in refractory patients (48% reduction in death). First-line phase 2 studies in BRAF mutant non-small cell lung cancer (close to 4% of the lung cancer population have BRAF mutations) should report out in 2022. First-line studies in colorectal cancers are ongoing with data from the phase 2 Anchor study likely in the second half of 2020. We view most of the opportunity in colorectal cancer (with upside in lung) as there are close to 200,000 colorectal patients with BRAF mutations per year in the developed world. At a price point of close to $250,000 annually, the opportunity is large.

Moat Trend and Product Pipeline

Product:		Tanezumab
Composition:		biologic (anti-NGF)
Economics:		50/50 profit split with Eli Lilly
Therapeutic Area:		pain
Launch Year/Probability		2020/55% in OA and 35% in back pain
2024 Sales	Morningstar	$665 million
	Consensus	$246 million
Market Model:		—

The two FDA clinical holds and J&J's 2016 decision to discontinue its NGF development program highlight the risks associated with this class of drugs and have led to close to zero in consensus sales expectations for the drug class, but the hold concerns have been addressed by further investigation. The phase 3 data has shown solid efficacy at high doses, but side effects of joint replacements (2% for placebo versus 4%-7% for tanezumab) and rapidly progressing osteoarthritis (0% versus 1%-2%) are concerning. Long term data in osteoarthrosis showed mixed data with positive efficacy with the 5mg dose (with worse side effects) and poor efficacy with the 2.5mg dose. The FDA and EMEA accepted the filing of the 2.5mg dose in March 2020. While we are concerned the FDA will not approve the drug based on the clinical data, we expect the drug will be widely used if approved given the limited options for pain management.

Product:		Abrocitinib/PF-04965842
Composition:		small molecule (JAK1 Inhibitor)
Economics:		—
Therapeutic Area:		atopic dermatitis
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	$700 million
	Consensus	$441 million
Market Model:		atopic dermatitis (p.164)

Phase 3 data showed EASI-75 response rates of 40-45% (100mg) and 61-63% (200mg), better than the market leader Dupixent's 44-51%. Also, in a head-to-head study, abrocitinib 200mg outperformed Dupixent on a secondary endpoint of itch. However, the serious adverse event rates seem a slightly little higher for abrocitinib (1-4% versus 1-3% for Dupixent). Pfizer is also running a study that starts with 200mg as a loading dose and then ramps down to 100mg, which should help with safety. Additionally, in the teen study (Jade Teen), the drug worked well at the 200mg dose, but only slightly at the 100mg level. The drug should be filed with regulators by the end of 2020.

Product:		Fidanacogene Elaparvovec
Composition:		biologic (Factor IX)
Economics:		royalties to Spark
Therapeutic Area:		hemophilia B
Launch Year/Probability:		2021/60%
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$216 million
Market Model:		hemophilia (p.173)

A phase 2 study in 15 hemophilia B patients showed annualized reduction in bleeding rates by 98% with no severe adverse events. Levels of factor IX were improved with an enhanced manufacturing process. A phase 3 study started in summer 2018 and should complete in 2021. UniQure's AMT-061 is on a similar phase 3 timeline with its modified therapy, which could have better efficacy than first-generation AMT-060 and prove competitive with Pfizer/Spark's therapy.

Product:		Ritlecitinib/PF-06651600
Composition:		Small molecule (JAK3/TEC Inhibitor)
Economics:		—
Therapeutic Area:		alopecia areata, ulcerative colitis
Launch Year/Probability:		2021/20%
2024 Sales	Morningstar	$462 million
	Consensus	$238 million
Market Model:		UC/Crohn's (p.168)

Pfizer is currently evaluating PF-06651600, its JAK3 inhibitor, in a phase 2/3 trial in Alopecia Areata (data 2021). A phase 2a study showed a 34-point change in SALT (Severity of Alopecia Tool) at 24 weeks with a p-value of less than 0.0001. The ultimate goal is that this drug can treat alopecia without the serious side effects of Xeljanz. The strong phase 2 results led to breakthrough status for alopecia. From a market standpoint, alopecia areata impacts close to 2% of the overall population[25] and pricing is likely close to immunology drugs for skin diseases like atopic dermatitis and psoriasis (close to $35,000 annually). The drug is also in midstage development for rheumatoid arthritis and ulcerative colitis with data likely in late 2020 or 2021, with phase 2 data in Crohn's likely by 2022.

25 Fricke, Alexandra. Epidemiology and Burden of Alopecia Areata: a Systematic Review, Clinical Comet July 2015.

Product:		PF-06425090
Composition:		vaccine
Economics:		—
Therapeutic Area:		C. difficile
Launch Year/Probability:		2021/80%
2024 Sales	Morningstar	$750 million
	Consensus	NA
Market Model:		—

Pfizer's vaccine was granted fast-track designation by the FDA in 2014. Pfizer's candidate is a three-dose recombinant vaccine, which is designed to stimulate an antibody against both toxins A and B produced by C. difficile. In Jan. 2017, the company released positive interim phase 2 trial data and began phase 3. Candidates received three doses of the vaccine on 1 of 2 schedules, and results showed the trial was safe and stimulated a C. difficile targeted immune response. The key phase 3 study should report in late 2020.

Product:		Brepocitinib/PF-06700841
Composition:		Small molecule (TYK2/JAK1 Inhibitor)
Economics:		—
Therapeutic Area:		alopecia areata, psoriasis, ulcerative colitis
Launch Year/Probability:		2023/40%
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$11 million
Market Model:		psoriasis (p.166), UC/Crohn's (p.168)

Pfizer is currently conducting midstage trials to evaluate the efficacy of the drug in patients with moderate to severe plaque psoriasis, psoriatic arthritis, Crohn's, ulcerative colitis, alopecia, lupus, atopic dermatitis, and several smaller immunology indications with phase 2 data expected to read out in early 2021.

Product:		PF-06826647
Composition:		Small molecule/TYK2
Economics:		—
Therapeutic Area:		psoriasis and IBD
Launch Year/Probability:		2023/40%
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$6.6 million
Market Model:		psoriasis (p.166), UC/Crohn's (p.168)

Pfizer is currently conducting midstage trials to evaluate the efficacy of the drug in patients with psoriasis (phase 2 data expected in 2020) and ulcerative colitis (phase 2 data expected in 2023).

Product:		SB-525
Composition:		Gene therapy
Economics:		—
Therapeutic Area:		Hemophilia A
Launch Year/Probability:		2023/40%
2024 Sales	Morningstar	$300
	Consensus	-
Market Model:		hemophilia (p. 173)

SB-525 could be solid competition for BioMarin, but we don't have the duration data to tell, and it will likely arrive on the market two years behind BioMarin's Roctavian. The first two patients at the high dose in the Ph 1/2 Alta study showed normal factor VIII levels at week 6 and consistent expression as of July 2019. As of December 2019, five patients were in the high-dose cohort, and one patient saw factor levels drop then rebound, while the rest looked steady, with the longest patient 44 weeks into treatment at this dose. As of June 2020, five patients in the high-dose cohort all had strong factor VII expression and no bleeds, with one patient 61 weeks into treatment at this dose (full 1-year data still to come). Pfizer started a lead-in study for phase 3 in October 2019 and expects to start a 63-pt phase 3 trial in H2 2020, with data 2022E.

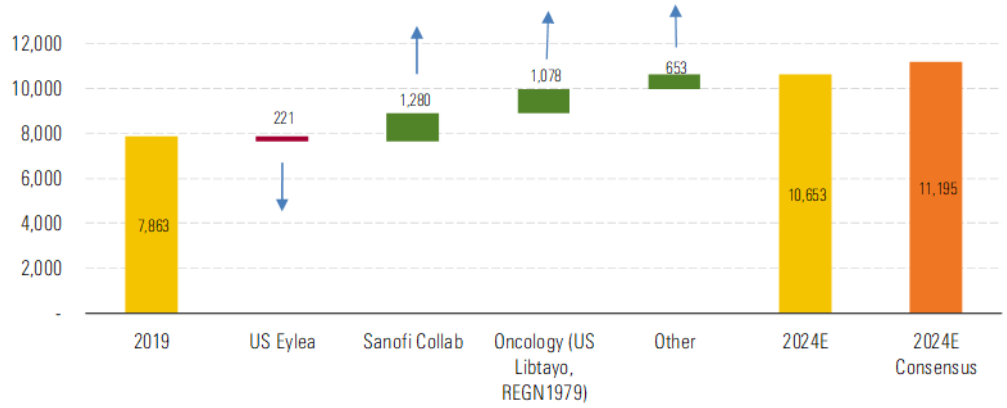
Product:		PF-06928316
Composition:		vaccine
Economics:		—
Therapeutic Area:		Respiratory Syncytial Virus (RSV)
Launch Year/Probability:		2024/40%
2024 Sales	Morningstar	Not material (in other sales)
	Consensus	$44 million
Market Model:		—

Phase 2 preliminary data was positive enough for Pfizer to start a phase 3 study in June 2020.

Regeneron REGN

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★	$473.00	1.33	Medium	Narrow	Positive

Revenue Breakdown USD Millions



Source: Morningstar, company reports, and DrugAnalyst, Visible Alpha for consensus.

Regeneron Facing Eylea Competition, but Dupixent's Growth and Pipeline to Relieve Pressure

Expiring Patents

We expect patent expiration for Eylea in the U.S. in 2024 (peak sales of $8 billion in 2023), assuming pediatric extension, although the enhanced importance of formulation safety for intraocular products could make biosimilar entry challenging. Momenta and Mylan are most advanced, with a phase 3 Eylea biosimilar. However, Eylea is also facing significant branded competition from Novartis (Beovu launched Q4 2019) and Roche (port delivery of Lucentis, antibody faricimab could launch 2021-22).

Inline Products

Regeneron's inline product growth potential is dominated by Dupixent. Dupixent's recent broad label in asthma should allow $4 billion in peak asthma sales, and we assume $4 billion in peak sales in the original atopic dermatitis indication. While Praluent's potential in cardiovascular disease has looked underappreciated, we think price concessions, share loss to Amgen, and upcoming competition from Novartis' inclisiran are concerning. Kevzara looks unlikely to gain significant share in arthritis, and we think Libtayo's late entry in the PD-1 market will prevent strong uptake as monotherapy.

Pipeline

Regeneron's late-stage pipeline could be at an inflection point. While we're more bearish on pain drug fasinumab (shared with Teva), which is likely generating key phase 3 data in osteoarthritis in 2020, we're more optimistic about Regeneron's oncology pipeline (led by CD20/CD3 bispecific REGN1979, Sanofi-partnered bispecifics targeting BCMA and MUC16, and a LAG3 antibody) and rare disease pipeline.

Moat and Product Portfolio

Expiring Patents

Product:		Eylea (aflibercept)
Composition:		biologic (VEGF fusion protein)
Economics:		Bayer (REGN holds U.S. rights, 50/50 split ex U.S.)
Therapeutic Area:		ophthalmology (wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy)
Patents/Generic Threats:		2024 U.S./2025 EU
2024 Sales:	Morningstar	$4.4 billion (U.S. Eylea)
	Consensus	$5 billion (U.S. Eylea)
Market Model:		—

Eylea sales are maturing and the drug is poised to face new competitive threats, but we think strong long-term data, approval for 12-week dosing in wet AMD in 2018, and approval in nonproliferative diabetic retinopathy in May 2019 will help Regeneron and partner Bayer maintain low-single-digit growth on average through 2024. Research on sustained release formulations (Ocular Therapeutix collaboration, 2016) and RNA interference in ophthalmology (Alnylam collaboration, 2019) could also extend Regeneron's ophthalmology franchise. We think Eylea will continue to slowly gain market share, growing from roughly $7.5 billion in global sales in 2019 (more than $4.5 billion U.S.) to peak sales of $8 billion by 2023 ($5.1 billion U.S.). We don't assume significant differentiation for the high-dose (8mg) version, which is entering phase 3 Pulsar in wet AMD and phase 3 Photon in DME this year (12 weeks and longer dosing intervals, as well as new formulation patents). Originally approved in wet AMD in 2011 (roughly 600,000 patients are treated for this disease in the U.S.), Eylea's recommended bimonthly dosing by intravitreal injection (directly into the eye) has a dosing advantage versus the once-monthly recommended dosing for key competitor, Roche/Novartis' Lucentis. Eylea expanded its indications into diabetic macular edema and macular edema following retinal vein occlusion in 2014, and the diabetic retinopathy subset of DME in 2015, allowing it to gain share from Lucentis. Eylea currently holds roughly 70% of the branded VEGF market in the U.S., with the remainder going to Lucentis (although repackaged Avastin, which is used off-label and significantly cheaper, accounts for close to half of volume). Key branded competitors will contribute to sales erosion, including Novartis' Beovu (FDA approved with 8 and 12-week dosing in wet AMD in Oct 2019, and Europe in Feb 2020), Roche's Lucentis port (phase 3 data in 2020 in AMD at 6-month dosing) and faricimab (potential 16-week dosing filing in 2021 in AMD), and gene therapies like Regenxbio's RGX-314 (entering phase 2 in 2020) and Adverum's ADVM-022 (phase 1 Optic data 2020). We expect the Talon study (comparing Beovu and Eylea head-to-head in wet AMD) should have data in 2022 that could further weigh on Eylea sales, although Beovu's issues with intraocular inflammation and reports of retinal vasculitis in Feb 2020 are concerning. We assume mid-single-digit erosion in price per patient beginning in 2019, due to slight reductions in doses per patient and competitive pricing (discounts began in June 2018). We expect biosimilars could enter in 2024, including Momenta/Mylan's M710 (in pivotal study in DME), Formycon/Santo's FYB203 (entering pivotal in H2 2020), and Biogen/Samsung's SB15 (phase 1). Eylea is heavily exposed to Medicare Part B (roughly half of revenue), but recent changes to step therapy in Medicare Advantage will only affect new patients, which limits the headwind. International benchmark pricing remains a risk, but we're skeptical of implementation, given Senate opposition.

Inline Products

Product:		Praluent (alirocumab)
Composition:		biologic (PCSK9 antibody)
Economics:		Beginning 2020, U.S. rights REGN, ex U.S. Sanofi (royalty to REGN)
Therapeutic Area:		cardiovascular (hypercholesterolemia)
Patents/Generic Threats:		2029 U.S./EU
2024 Sales:	Morningstar	$400 million (U.S. REGN sales)
	Consensus	$250 million
Market Model:		—

We think Praluent could benefit the millions of patients whose disease is still uncontrolled with statins, but we've lowered our peak sales estimate to roughly $1 billion given Repatha's stronger launch (partly tied to uncertainty around Praluent's infringement on Repatha patents) and the potential entry of new cholesterol-lowering competitors, such as Novartis/Medicines Company's PCSK9 therapy inclisiran (late 2020 launch expected) and Esperion's cheaper oral ACL inhibitor Nexletol/bempedoic acid (approved Feb 2020). Complete data from Praluent's cardiovascular safety in 2018, matching Amgen's over 15% CV risk reduction and achieving a 22% reduction in risk of death (label expanded in April 2019), does support extended payer coverage after an initial slow ramp. Continued price competition with Amgen has also hit our sales estimates, as new lower list price versions of both Repatha and Praluent have triggered reassessment of PBM contracts. Regeneron locked in an exclusive deal with Express Scripts in 2018 based on cost-effective pricing ranges found in an ICER analysis, although the 2020 preferred formulary includes both Repatha and Praluent.

Product:		Kevzara (sarilumab)
Composition:		biologic (IL-6 antibody)
Economics:		Sanofi (50/50)
Therapeutic Area:		rheumatoid arthritis
Patents/Generic Threats:		2028 U.S./2027 EU
2024 Sales:	Morningstar	EUR 475 million (Global Sanofi sales)
	Consensus	EUR 550 million (Global Sanofi sales)
Market Model:		RA (p.167)

Despite superiority data to Humira, Kevzara is relatively undifferentiated from Roche's blockbuster Actemra, and we've lowered our peak sales estimate to $500 million from $1 billion. Kevzara was approved in May 2017 with a list price set at $39,000 a year for both doses, roughly the same as net prices for TNF drugs Humira and Enbrel, and relatively similar to Actemra's pricing. Kevzara also entered a trial as a treatment for hospitalized patients with COVID-19 in March 2020, but initial results were disappointing, and after failing to see a significant benefit over placebo in severely-ill patients, the trial was subsequently narrowed to the higher 400 mg dose and more advanced, critically ill patients. The trial failed in this setting as well in July 2020; the 400 mg dose produced a positive trend in mechanically ventilated at baseline, but a negative trend in patients not mechanically ventilated at baseline. Regeneron is stopping the 800 mg arm as a result, but an ex US trial continues, with data expected in the third quarter.

Product:		Dupixent (dupilumab)
Composition:		biologic (IL4/IL13 antibody)
Economics:		Sanofi (50/50)
Therapeutic Area:		asthma, atopic dermatitis
Patents/Generic Threats:		2031 U.S./2032 EU
2024 Sales:	Morningstar	EUR 7.1 billion (Global Sanofi sales)
	Consensus	EUR 7.1 billion (Global Sanofi sales)
Market Model:		atopic dermatitis (p.164), biologic respiratory (p.171)

We assume $10 billion in peak Dupixent sales, roughly in-line with Sanofi's peak sales goal of more than EUR 10 billion, based on the drug's solid safety and efficacy profile in atopic dermatitis ($4 billion peak) that should withstand incoming competition, superior profile and broader potential in asthma ($4 billion peak) than IL5 antibodies Nucala and Fasenra, as well as expansion into smaller immunology indications over the next two years (total of $1 billion peak) with relatively convenient bi-weekly subcu dosing. Sales are already annualizing north of $3 billion a year, and Dupixent only has a single-digit share of biologics-eligible patients in atopic dermatitis and asthma indications, implying plenty of room to grow.

Sanofi and Regeneron received approval in March/September 2017 in the U.S./Europe in adult atopic dermatitis, and October 2018 in the U.S. in moderate to severe asthma in patients age 12 and up who either have high eosinophil counts (similar to IL-5 labels) or are uncontrolled on oral corticosteroids (differentiated from other biologics). In atopic dermatitis, Regeneron is targeting the 300,000 adults in the U.S. with the most severe disease, gradually expanding approval to smaller but significant populations in adolescents (2019) and pediatric groups of age 6 and up (2020) and six months and up (2022E). In asthma, there are 900,000 moderate to severe patients in the U.S. who are uncontrolled and eligible for biologic treatments, and Dupixent is likely to expand approval to children 6 and up by 2022 (phase 3 data by the end of 2020).

Beyond atopic dermatitis and asthma, Dupixent has numerous other opportunities in the immunology space. Dupixent was approved in June 2019 in patients with nasal polyps (250,000 surgeries in U.S. and EU5 annually). It is also in pivotal studies in eosinophilic esophagitis (phase 2 data was positive in May 2020, phase 3 data 2022E, 160,000 patients in the U.S. alone) and in skin conditions like chronic spontaneous urticaria (hives, 150,000 not responding to current treatment in U.S., 2022E submission), prurigo nodularis (74,000 eligible in U.S., 2021E submission), and bullous pemphigoid (27,000 treated with steroids in the U.S., 2023E submission). We don't model additional indications that could lead to upside, such as the phase 3 COPD program (300,000 in U.S. in need of new treatments, but high-risk development area, 2024E submission) and mid-stage studies in peanut and grass allergies (peanut allergy trial with Aimmune to have data in 2020).

We expect oral JAK inhibitors could be a longer-term threat in atopic dermatitis, as phase 3 data for AbbVie's Rinvoq and Pfizer's abrocitinib looked better than Dupixent at high doses, and both will have head-to-head data against Dupixent (abrocitinib saw faster itch control in March 2020, with more details later in 2020, and Rinvoq head-to-head data is due in first-quarter 2021) . Eli Lilly's IL13 lebrikizumab (phase 3 data 2021E) could improve on Dupixent's safety and convenience. Strong phase 2 data from Amgen/Astra's tezepelumab could make this is a solid long-term competitor in asthma (phase 3 data late 2020E), although the drug's atopic dermatitis data has been disappointing.

Product:		Libtayo (cemiplimab/REGN2810)
Composition:		biologic (PD-1 antibody)
Economics:		Sanofi IO collaboration (50/50), REGN books U.S. sales, 8% royalty to BMY/Ono through 2023
Therapeutic Area:		cutaneous squamous cell carcinoma, BCC, NSCLC, cervical cancer
Patents/Generic Threats:		U.S. 2035
2024 Sales:	Morningstar	$600 million (U.S. REGN sales)
	Consensus	$950 million (U.S. REGN sales)
Market Model:		immuno-oncology (p.181)

Regeneron is significantly behind other players in the PD-1 antibody market (Bristol and Merck have leading market shares, and PD-L1 therapies from Roche, Astra, and Pfizer have all entered the market), and we're skeptical of Libtayo's ability to differentiate. The drug was approved in the U.S. based on a phase 2 pivotal trial in advanced cutaneous squamous cell carcinoma (second-deadliest skin cancer, high mutation rate) in 2018. We include moderate sales for the drug in this niche indication (where it had gained 48% share of the U.S. market by the end of first quarter 2020), where it produces improving complete responses over time (16% as of ASCO 2020), although Merck received approval of Keytruda in this indication (based on data from Keynote-629) in June 2020. Regeneron plans to file in basal cell carcinoma and first-line PDL1-positive NSCLC later in 2020. Data in PD-L1 positive NSCLC patients (PD-L1 on at least half of tumor cells, or 25-30% of diagnoses) showed an ORR of 42% for Libtayo (versus 22% chemo), and the trial was stopped early at an interim survival analysis that showed a 32.4% reduction in risk of death versus chemo. This looks like strong efficacy on par with approved treatments from Roche and Merck, particularly given the fact that a third of patients in the trial enrolled in the last six months (less likely to see significant survival benefit yet) and that all chemotherapy patients are allowed to crossover to the Libtayo arm when they progress (blurring the distinction between the two arms). Regeneron still enrolling a larger phase 3 program with Libtayo in various combinations—a lung cancer trial in combination with chemotherapy should complete enrollment this year (data 2021). We expect Regeneron's potential for differentiation comes from novel combinations. The drug is also in phase 3 in cervical cancer (to file 2021) and in early-stage studies with Sanofi's CD38 antibody Sarclisa, Regeneron's LAG3 antibody REGN3767 (data 2021), and with internal bispecifics like CD20/CD3 REGN1979 (lymphoma data 2020), CD28/PSMA REGN5678 (prostate cancer data 2024), and MUC16 REGN4018 (ovarian cancer data 2022). Regeneron also entered collaborations to expand its midstage combination therapy trials, combining Libtayo with Inovio's INO-5401 and INO-9012 in brain cancer, SillaJen's Pexa-Vec in kidney cancer, ISA's ISA101b in head and neck cancers, and Vyriad's oncolytic virus Voyager-V1 in multiple tumor types.

Moat Trend and Product Pipeline

Product:		fasinumab (REGN475)
Composition:		biologic (nerve growth factor antibody)
Economics:		Teva 50/50, Mitsubishi (Asia)
Therapeutic Area:		pain (osteoarthritis)
Launch Year/Probability:		2022/30%
2024 Sales:	Morningstar	$290 million
	Consensus	no estimate
Market Model:		—

There is a significant opportunity for an alternative to addictive opioids to address chronic pain, but safety issues have prevented higher-efficacy dosing of NGF-targeted drugs, limiting their potential for approval or commercial uptake. Initial phase 3 osteoarthritis data in August 2018 was positive, with significant reductions in pain and improvements in function compared with placebo after 16 weeks, and data from larger safety and efficacy studies in osteoarthritis for fasinumab are likely in 2020 (filing expected in 2021). However, similar pain antibody tanezumab from Pfizer and Eli Lilly reported disappointing phase 3 data in early 2019, with modest efficacy (lower 2.5mg dose failed to achieve significance) and continued serious side effects (high dose saw 6% of patients with rapidly progressive osteoarthritis), and we lowered our probability of approval for fasinumab to 30% from 55% as a result. While the drug appears to be at least a year behind Pfizer/ Eli Lilly's tanezumab (which was filed with the FDA in Dec 2019), we still think this is a nearly $1 billion opportunity (roughly 25% of a $3 billion market in 2028), although Regeneron partnered with Teva to help spread development costs and reduce risk. Regeneron was forced to discontinue higher doses of fasinumab due to risk benefit concerns (including the entire lower back pain phase 3 study), and lower doses may not prove effective enough. The NGF class was put on clinical hold twice by the FDA due to concerns over safety (osteonecrosis and neuronal cell death), but following additional data and debate, fasinumab re-entered clinical development in 2015.

Product:		REGN1979
Composition:		biologic (CD20/CD3 bispecific)
Economics:		—
Therapeutic Area:		lymphoma
Launch Year/Probability:		2022/60%
2024 Sales:	Morningstar	$540 million
	Consensus	$340 million
Market Model:		NHL (p.185)

While early data began to emerge at ASH 2016 for this product, dose escalation has continued in an effort to find the dose that maximizes safety while reducing safety issues, and recent data at ASH 2019 was impressive. Updated data at ASH 2019 in patients taking at least 5 mg doses showed a 96% ORR and 77% CR in 22 patients with FL, and in the 19 DLBCL patients taking at least 80 mg doses, ORR was 58% and CR 42% (including a 25% CR for 12 patients receiving prior CAR-T therapy). Regeneron entered a multi-arm pivotal phase 2 study in 2019 which could serve as the basis for approval in FL and DLBCL, and Regeneron hopes to complete enrollment in 2021 and file for approval in 2022. Regeneron is also studying REGN1979 in combination with Libtayo, although side effects (cytokine release syndrome and two potentially related deaths) from this combination could limit use unless dose modifications resolve the issue. Regeneron also expects to move into earlier lines of NHL treatment with chemotherapy combination trials starting in 2020. Roche is aggressively pursuing its own CD20 bispecifics, but efficacy in pivotal trials will be key for comparisons. Genmab's GEN3013 (epcoritamab) is in dose expansion in phase 1/2 testing, with data and potential initiation of pivotal programs in 2020.

Product:		REGN5458/5459
Composition:		Bispecific antibodies (BCMA/CD3 bispecifics)
Economics:		Sanofi opt-in rights at POC (50/50 global rights)
Therapeutic Area:		Multiple myeloma
Launch Year/Probability:		2023/40%
2024 Sales:	Morningstar	$500 million
	Consensus	NA
Market Model:		MM (p.188)

Regeneron's BCMA-targeting bispecific antibodies have advanced quickly. REGN5458 has an encouraging safety profile so far with no neurotoxicity, and while cytokine release syndrome was seen in 3 patients, none were grade 3 or higher. A multi-arm pivotal phase 2 study began in early 2019 that should generate data by 2022, but we expect additional interim updates later this year (likely at ASH 2020) and the potential start of pivotal studies in late 2020. ASH 2019 data for the first two doses (3mg and 6mg weekly) in patients with a median of 7 prior lines of therapy showed 75% response in the 6mg group (3 of 4 patients) and 2 of these (50%) were MRD negative. Regeneron is now testing higher doses and has started a trial for REGN5459, which has different CD3 binding affinity. Key BCMA bispecific competitors include J&J's teclistamab and Amgen's AMG 701, both of which are also in dose-finding studies and could see once-weekly dosing.

Product:		evinacumab
Composition:		biologic (ANGPTL3 antibody)
Economics:		Royalties to Sanofi (did not opt in)
Therapeutic Area:		Homozygous familial hypercholesterolemia
Launch Year/Probability:		2021/70%
2024 Sales:	Morningstar	$150 million
	Consensus	$100 million
Market Model:		—

HoFH is a rare, inherited form of high cholesterol that isn't always responsive to statins or even PCSK9 therapy. Regeneron plans to file for approval of evinacumab in 2020 based on strong data, with a 49% drop in LDL at 24 weeks compared to placebo (from an average of 255mg/dL at the start of the trial, despite the use of statins in 95% of patients and PCSK9 in 79% of patients). RNA-based drugs from Arrowhead (ARO-ANG3) and Ionis/Pfizer (vupanorsen) are also targeting ANGPTL3 and in mid-stage development, but speed of development in this rare niche is unclear, as both products are likely being moved forward in broader populations with high LDL and triglyceride levels.

Product:		garetosmab (REGN2477)
Composition:		biologic (Activin A antibody)
Economics:		Royalties to Sanofi (did not opt in)
Therapeutic Area:		FOP (fibrodysplasia ossificans progressiva)
Launch Year/Probability:		2021/60%
2024 Sales:	Morningstar	$120 million
	Consensus	no estimate
Market Model:		—

FOP is a debilitating ultra-orphan disease (800 diagnosed worldwide) that causes tissue to be replaced with bone, and garetosmab produced solid phase 2 data in adults in early 2020 that could form the basis of approval, following additional data from the second half of the study later in 2020. In the Lumina-1 study, Regeneron did not see statistically significance on the primary endpoint of total lesion activity (which was 25% lower than the placebo arm), but a 90% reduction in new bone lesions was a compelling result, particularly as Regeneron plans to move the drug into pediatric studies.

Product:		REGN-COV2
Composition:		Antibody cocktail
Economics:		—
Therapeutic Area:		SARS-CoV-2
Launch Year/Probability:		2020/60%
2024 Sales:	Morningstar	— ($2 billion annual sales, 2021-22)
	Consensus	—
Market Model:		—

Regeneron started two clinical studies for antibody cocktail REGN-COV2 in June, focused on 1,850 hospitalized patients and 1,050 non-hospitalized patients in the U.S., Brazil, Mexico, and Chile, and Regeneron expects data later this summer. Regeneron is also conducting a prevention study with NIAID beginning in July, with 2,000 volunteers who have had close exposure to diagnosed patients in the U.S. However, without clinical data (or any guidance for management on initial pricing), it's difficult for this program to move the meter substantially on our valuation. We assume emergency use could begin in the fall, with official approval at the end of the year. Regeneron is quickly ramping manufacturing capacity for the cocktail and will potentially supply millions of doses per month from its New York facility by 2021. Regeneron initially cited capacity for 200,000 prevention doses (or 20,000 treatment doses) per month by August, but the $450 million BARDA contract announced in July 2020 gives the U.S. government access this fall to 420,000-1.3 million doses for prevention or 70,000-300,000 doses for treatment, depending on chosen doses. We still assume $2 billion in potential sales in 2021 and 2022, similar to our model for Gilead's remdesivir. Several other antibody programs are entering testing, but Regeneron's program is distinguished from most with its cocktail strategy, which in preclinical testing (data published mid-June) appears to prevent the virus from escaping the efficacy of the antibodies.

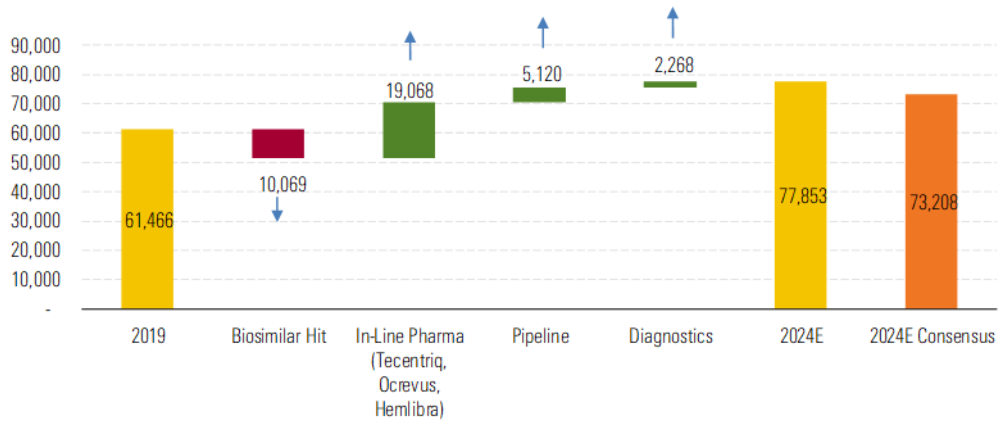
Product:		pozelimab (REGN3918)
Composition:		biologic (C5 antibody)
Economics:		Royalties to Sanofi (did not opt in)
Therapeutic Area:		PNH (paroxysmal nocturnal hemoglobinuria)
Launch Year/Probability:		2023/60%
2024 Sales:	Morningstar	$100 million
	Consensus	no estimate
Market Model:		—

Regeneron is starting a phase 3 trial in PNH in the second half of 2020, as well as a combination trial with Alnylam's cemdisiran. Positive phase 2 data for pozelimab in six patients was reported in Dec 2019; a weekly 800mg subcu dose of pozelimab allowed patients to achieve normal LDH levels by week 8. LDH is a biomarker for elevated hemolysis, or abnormal destruction of red blood cells that defines this rare disease. The second cohort of the phase 2 trial, in 30 patients, is ongoing. Regeneron's goal is to give patients more complete blockade of complement activation than current standard of care (Alexion's Soliris and Ultomiris) as well as convenient subcu dosing. Combination with Alnylam's cemdisiran could improve efficacy or allow less frequent dosing. We think competing with Alexion's dominant established franchise with Soliris (every two-week infusions), Ultomiris (every two-month infusions), and improved subcu dosing of Ultomiris (phase 3 once weekly data expected in 2020, approval by 2022) is a high bar, but see combination with Alnylam's RNAi therapy as a potential differentiator.

Roche RHHBY

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★★	$54.00	0.81	Low	Wide	Stable

Revenue Breakdown CHF Millions



Source: Morningstar, company reports; DrugAnalyst, Visible Alpha for consensus.

Tecentriq, Ocrevus, Hemlibra Offset Biosimilar Hit, With Oncology/Neurology Pipeline Upside

Expiring Patents

Roche's top three biologics--Rituxan, Herceptin, and Avastin (32%, or CHF 20 billion, of 2019 sales)--should see an additional CHF 10 billion hit to sales through 2024 (CHF 4 billion in 2020 alone) as biosimilar launches continue globally. Roche has limited exposure to small-molecule patents (Esbriet 2022). Actemra and Xolair could see limited biosimilar launches over the next couple of years.

Inline Products

Roche is extending old franchises with new products, and Perjeta and Kadcyla (breast cancer) as well as Venclexta, Gazyva, and Polivy (blood cancer) have patent protection until at least 2025. While PD-L1 antibody Tecentriq arrived third to market, we think it holds significant potential in lung cancer (liver metastases, EGFR/ALK mutations, SCLC), with Avastin in liver cancer, and with novel drugs (TIGIT-targeting tiragolumab), and we model sales of CHF 11 billion by 2024. MS drug Ocrevus and hemophilia drug Hemlibra are differentiated multibillion-dollar franchises that diversify Roche away from oncology.

Pipeline

Roche has a large late-stage pipeline, with potential launch dates in 2020 (SMA drug risdiplam, NMOSD drug satralizumab) and 2021 (including IBD drug etrolizumab, breast/prostate cancer drug ipatasertib, and Huntington's treatment RG6042) followed by a solid long-term pipeline. We're particularly watching potential 2022 launches in oncology (CD20/CD3 bispecifics), neurology (Alzheimer's antibody gantenerumab and DMD gene therapy RG6356), and ophthalmology (Lucentis port delivery and faricimab).

Moat and Product Portfolio

Expiring Patents

Product:		Rituxan/Mabthera
Composition:		biologic (CD20 antibody)
Economics:		—
Therapeutic Area:		oncology (NHL/CLL), arthritis
Patents/Generic Threats:		expired (2025+ subcu)
2024 Sales:	Morningstar	$2.7 billion
	Consensus	$2.5 billion
Market Model:		CLL (p.187), NHL (p.185)

Rituxan sales are in decline, as sales either transfer to Roche's next-generation CD20 antibody Gazyva (Gazyva proved superior in CLL and indolent NHL, which represent a little over half of Rituxan sales) or remain vulnerable to biosimilar competition (25% of Rituxan sales are in aggressive lymphoma, where Gazyva failed to show superiority to Rituxan, and 20% of Rituxan sales are outside of oncology, where Roche did not test a follow-on drug). In the U.S., Teva's Truxima launched in Nov 2019, followed by Pfizer's Ruxience in Jan 2020 (at a 24% discount). A subcutaneous version of Rituxan, Rituxan Hycela, was approved in 2017 in the U.S., reducing administration time from 1.5 hours to 5-7 minutes, although uptake has been limited, and we expect this to offer little protection to Rituxan sales. In Europe, Celltrion/Teva's Truxima (approved February 2017) and Novartis' Rixathon (approved June 2017) drove a 46% decline in Rituxan's Europe sales in 2018 and a 36% decline in 2019 (Roche had minimal entrenchment with subcutaneous Rituxan in Europe). Rituxan's addition to China's national reimbursed drug list in 2017 boosted volume growth, but biosimilars should weigh on sales in this region as well (the first biosimilar was approved in Feb 2019).

Product:		Herceptin
Composition:		biologic (HER2 antibody)
Economics:		—
Therapeutic Area:		HER2+ breast, gastric cancers
Patents/Generic Threats:		Expired 2025+ subcu 2030+ Perjeta co-formulation Phesgo
2024 Sales:	Morningstar	$3.3 billion
	Consensus	$2.9 billion
Market Model:		—

Today, roughly 70% of Herceptin sales are in early breast cancer (a mix of neoadjuvant and adjuvant), and patients typically either receive both neoadjuvant and adjuvant treatment or only adjuvant treatment. Herceptin use in the adjuvant setting is already concentrated in high-risk patients, where Roche had the strongest data in the Aphinity study testing the Herceptin/Perjeta combination. A subcutaneous coformulation of Herceptin and Perjeta, termed Phesgo, can be administered in five minutes (versus 1-2.5 hours for the IV combination), and Phesgo received FDA approval in June 2020. This likely extends Roche's IP to 2030, but lower pricing will be key to preserving share in the face of biosimilar Herceptin competitors. In Europe, biosimilar competition rapidly ramped up in 2018, led by Samsung/Merck (Ontruzant approved November 2017), Celltrion/Teva (Herzuma, February 2018), Amgen/Allergan (Kanjinti, June 2018), and Pfizer (Trazimera, July 2018). Entrenched subcutaneous Herceptin (roughly 50% market share) and the need for Perjeta combination therapy have failed to limit Europe market erosion, with sales down 45% in 2019. In the U.S., we don't expect Roche's Hylecta (subcutaneous Herceptin launched in 2019) to significantly protect sales, as Amgen launched Kanjinti in July 2019 at a 15% discount, followed by Mylan's Ogivri in Dec 2019, Pfizer's Trazimera (22% discount) in Feb 2020, Teva/Celltrion's Herzuma (10% discount) in March 2020, and Samsung/Merck's Ontruzant (15% discount) in April 2020. We expect solid U.S. uptake, but declines should take time as patients are unlikely to switch during treatment (many patients take one year of Herceptin). Volume growth in China since Herceptin was added to the national reimbursed drug list in 2017 has supported growth, but Henlius has filed biosimilar HLX02 in Europe and China, and we expect further competition to push international Herceptin sales growth into negative territory in 2021.

Product:		Avastin
Composition:		biologic (VEGF antibody)
Economics:		—
Therapeutic Area:		various oncology
Patents/Generic Threats:		2019 U.S./2020 EU
2024 Sales:	Morningstar	$3.5 billion
	Consensus	$3 billion
Market Model:		—

Sales are driven by colorectal cancer maintenance and new indications like ovarian and cervical cancers, and while Avastin will see combo use with Tecentriq (December 2018 Tecentriq label expansion into first-line NSCLC), biosimilars began to weigh on sales beginning in late 2019 in the U.S. Most of the drug's lung cancer sales are at risk from recent launches of immuno-oncology therapies (especially Merck's Keytruda), as are a small percentage of colorectal cancer sales (15% of patients who are MSI-high), and PD-1 antibodies are gaining approval in other areas like kidney and ovarian cancer. This is likely to push Avastin back to later lines of therapy or potentially make Avastin a part of combination therapy. Among biosimilar entrants, Amgen has a clear lead, with Mvasi launched in the U.S. in July 2019 and Pfizer's Zirabev launched in early 2020 (at a 23% discount to branded Avastin). Slower biosimilar progress in other international markets with high demand could allow continued volume growth in these regions; Avastin was added to China's national reimbursed drug list in 2017, although China just saw its first biosimilar Avastin approval in Dec 2019.

Product:		Esbriet
Composition:		small molecule
Economics:		—
Therapeutic Area:		idiopathic pulmonary fibrosis (IPF)
Patents/Generic Threats:		2022 U.S./2021 EU
2024 Sales:	Morningstar	$300 million
	Consensus	$600 million
Market Model:		—

Esbriet's U.S. uptake is going well, and mortality benefit data and underpenetration in mild to moderate patients have given the drug continued growth, despite competition from Boehringer's Ofev.

Product:		Xolair
Composition:		biologic (IgE antibody)
Economics:		U.S. co-prom. w/Novartis (Novartis ex-US rights)
Therapeutic Area:		moderate to severe asthma, hives, nasal polyps
Patents/Generic Threats:		2018 U.S.
2024 Sales:	Morningstar	$1.3 billion
	Consensus	$1.5 billion
Market Model:		biologic respiratory (p.171)

Xolair sales are growing strongly with the new hives indication (2014), but Novartis' phase 3 antibody ligelizumab proved superior in this indication in a recent phase 2 study (filing and phase 3 data expected in 2021). New branded competition (such as Glaxo's Nucala and Sanofi/Regeneron's Dupixent) are also likely to affect long-term growth in the core asthma indication. Xolair could theoretically be vulnerable to biosimilars due to patent expirations, but the biosimilar landscape looks relatively limited, with Glenmark targeting entry in 2022 (Roche doesn't expect biosimilars until at least 2023). Xolair in prefilled syringes became available in early 2019, improving convenience over reconstituted vials. Roche filed for approval in patients with nasal polyps in 2019 (approval expected by 3Q 2020) and has moved the drug into phase 3 testing in food allergies, mirroring indications already being pursued by competing drug Dupixent (which was approved for treatment of nasal polyps in June 2019).

Product:		Actemra/RoActemra
Composition:		biologic (IL-6 antibody)
Economics:		—
Therapeutic Area:		rheumatoid arthritis, COVID-19
Patents/Generic Threats:		2019 U.S./2018 EU
2024 Sales:	Morningstar	$2.3 billion
	Consensus	$2.6 billion
Market Model:		RA (p.167)

Actemra's strong efficacy as a single agent RA treatment boosted market share in Europe, and subcutaneous delivery expands share in the U.S. A competing IL-6 launch (Sanofi and Regeneron's Kevzara launched at a similar price to Actemra) has failed to generate significant market share erosion, and there are few biosimilars on our radar (Roche doesn't expect a biosimilar launch until at least late 2022). Therefore, we model gradual, single-digit declines to Actemra sales over our 10-year forecast period. Roche is also studying Actemra as a treatment for patients with COVID-19, and we've slightly increased our near-term assumptions due to use of the drug beginning in early 2020. Data from 450-patient phase 3 studies Covacta (in combination with standard of care) and Remdacta (in combination with remdesivir) should be available in summer 2020. Roche is making millions of doses to prepare for potential further use and received emergency authorization for the Elecsys test of IL-6 (an early marker of severe inflammation) in June.

Inline Products

Product:		Gazyva
Composition:		biologic (CD20 antibody)
Economics:		—
Therapeutic Area:		oncology (NHL/CLL), lupus
Patents/Generic Threats:		2030 U.S./EU
2024 Sales:	Morningstar	$1.8 billion
	Consensus	$1.4 billion
Market Model:		CLL (p.187), NHL (p.185)

Glycoengineered antibody Gazyva is more effective than Roche's established CD20 antibody Rituxan in CLL and indolent NHL, covering approximately 70% of Rituxan's oncology usage. While the drug failed to prove superior to Rituxan in DLBCL, approval and NCCN guideline support of Gazyva's superiority in the first-line follicular lymphoma setting should accelerate sales growth beyond 2018. We see combination use with Venclexta in first-line CLL (approved based on the CLL14 study with a 0.33 PFS hazard ratio against Gazyva/chlorambucil in May 2019) as a potential way to avoid chemotherapy and convert more patients to Roche's next-generation product. In addition, combination use with BTK inhibitors should support Gazyva use in first-line CLL, including an Imbruvica/Gazyva regimen (approved based on the illuminate study, with a 0.15 hazard ratio against Gazyva/chlorambucil, in January 2019) and Calquence/Gazyva (0.10 hazard ratio in Elevate-TN at ASH 2019). However, a phase 3 trial of Imbruvica/Venclexta (data 2021E) could create a fixed-duration competitor that removes a CD20 from upfront treatment in CLL. Despite prior failures for CD20 therapies in lupus, Gazyva showed strong data in lupus nephritis in the phase 2 Nobility study, with 40% complete renal response versus 18% for the control arm and very strong safety. Roche is moving forward into phase 3 trials. However, Glaxo's Benlysta saw positive data in December 2019 in lupus nephritis (primary efficacy renal response over two years of 43% versus 32% for placebo) and is poised to file for label expansion in 2020, making it likely to be first to market. Aurinia's voclosporin (filed with FDA in May 2020, based on renal response of 41% versus 22.5% in the control arm) is also a competitor. Roche estimates that lupus nephritis affects 190,000 lupus patients in the U.S. and Europe each year.

Product:		Perjeta
Composition:		biologic (HER2/HER3 antibody)
Economics:		—
Therapeutic Area:		HER2+ breast cancer
Patents/Generic Threats:		2025 U.S./EU 2030+ Herceptin co-formulation Phesgo
2024 Sales:	Morningstar	$4.7 billion
	Consensus	$5.5 billion
Market Model:		—

We expect Perjeta to continue to form the basis of Roche's pricing power in HER2-positive breast cancer and are particularly focused on its use as part of a subcutaneous fixed-dose combination (FDA approved as Phesgo in June 2020--patent protection through at least 2030) and potential use with Kadcyla in the adjuvant setting (Kaitlin data 2020E). Perjeta is established as standard of care in combination with Herceptin in patients with early-stage (neoadjuvant setting, prior to surgery, based on the Neosphere study) or advanced (metastatic setting, based on the Cleopatra study) HER2-positive breast cancer. Data for Herceptin and Perjeta in the adjuvant setting (following surgery in early-stage disease) from the Aphinity study in 2017 was disappointing, with disease-free survival at three years of 93% for Herceptin versus 94% for the combination, and we expect adjuvant use of the combination will be most common in the U.S. and in higher-risk patients (either node positive or hormone receptor negative) that account for roughly 75% of early-stage, HER2-positive patients. Roche received approval for high-risk patients in December 2017. Data in these patients was significantly better, with disease-free survival rates for the combination roughly 2 percentage points above standard Herceptin therapy. An updated Aphinity analysis in 2019 showed six-year disease-free survival at roughly 91% versus 88% for Herceptin and chemo alone, showing that the relative benefit increases with time and that this is a high bar for any would-be competitors in the early-stage HER2-positive breast cancer market.

Product:		Tecentriq/atezolizumab
Composition:		biologic (PD-L1 antibody)
Economics:		—
Therapeutic Area:		various cancers
Patents/Generic Threats:		2029 U.S./EU
2024 Sales:	Morningstar	$11.3 billion
	Consensus	$6.4 billion
Market Model:		immuno-oncology (p.181)

While Roche is third to market behind PD-1 antibodies (Bristol's Opdivo and Merck's Keytruda), we think the drug will achieve roughly $11 billion in sales by 2024, or 20% of the global $54 billion PD-1/PD-L1 market. We expect two thirds of Tecentriq sales will come from lung cancer, a combination of nonsquamous NSCLC, SCLC, and early NSCLC (adjuvant/neoadjuvant trials should have data by early 2021). In nonsquamous NSCLC, Tecentriq was approved in combination with Avastin and chemo in December 2018 and has differentiated data in patients with ALK/EGFR mutations or liver metastases. We think this will make up the bulk of Tecentriq's metastatic NSCLC usage in the near term, as the Tecentriq/chemo combination approved in December 2019 doesn't look competitive with Merck's entrenched Keytruda/chemo regimen, and Impower110 data for Tecentriq as monotherapy in PD-L1 positive NSCLC patients (approved May 2020) looks similar to Keytruda's data in this setting, making it difficult gain share from a heavily entrenched competitor. That said, combination with Roche's novel TIGIT antibody tiragolumab looks promising, and this combo could launch as early as 2023 in lung cancers. In SCLC, Roche was first to market in the first-line setting with a March 2019 FDA approval, and this represents roughly 15% of new lung cancer patients; Merck's failure to achieve an OS benefit in this indication could boost Roche's ability to maintain strong share, although Imfinzi's survival benefit led to approval of Astra's drug in March 2020. Beyond lung cancer, Roche was also first to market with Tecentriq in metastatic triple-negative breast cancer (approval in PD-L1-positive patients in March 2019) and had positive data in BRAF-positive melanoma (in combination with Zelboraf and Cotellic), but we see these markets as highly competitive (Merck met a PFS endpoint in mTNBC KN-355 in February 2020). Roche recently filed for approval in liver cancer (approved in the U.S. in May 2020, filed in Europe and China) and melanoma, and Roche is poised to file for additional approvals in neoadjuvant triple-negative breast (positive top line June 2020) and ovarian cancer (if data are positive in 2020); we're particularly bullish on Avastin combinations in liver and ovarian cancers. Roche reported positive phase 3 liver cancer data in November 2019, showing a 42% reduction in the risk of death over standard treatment Nexavar (overall survival not reached versus 13.2 months for Nexavar), and the liver cancer opportunity is particularly pronounced in China (120,000 patients are treated in this market, versus about 20,000 in the U.S. and Europe combined). We're watching for potential competition from Astra, as the phase 3 Himalaya study (Imfinzi/tremelimumab) should have data in 2020 in first-line liver cancer, and the combination produced overall survival of 18.7 months in an uncontrolled phase 2 in second-line HCC at ASCO 2020. Merck's Keytruda and Lenvima combination had positive data in phase 1b Keynote-524 at ASCO 2020 (36% response rate, 12.6-month duration of response, and 22-month overall survival), with phase 3 data expected in 2022 from Leap-002.

Product:		Venclexta/venetoclax, GDC/ABT-199
Composition:		small molecule (Bcl-2 inhibitor)
Economics:		50/50 profit split (AbbVie books sales)
Therapeutic Area:		CLL, AML, MM, MDS
Patents/Generic Threats:		2031 U.S./EU
2024 Sales:	Morningstar	$2.9 billion
	Consensus	$2.8 billion
Market Model:		CLL (p.187), multiple myeloma (p.188), NHL (p.185)

Venclexta was initially approved in a subset of CLL patients with the 17p deletion, but approval was extended in 2018 to relapsed/refractory CLL (higher PFS and OS with Venclexta/Rituxan than with the prior standard of care, Rituxan and bendamustine, in the Murano study) and to first-line CLL in 2019 (Gazyva/Venclexta combination had a hazard ratio of 0.33, or 67% PFS risk reduction, in the CLL14 study versus Gazyva plus chemo, in patients with co-existing conditions). Venclexta is boxed out of some combinations, like CD20/BTK combos; Gazyva/Imbruvica was approved in a similar setting in January 2019 (illuminate study showed hazard ratio of 0.23 versus Gazyva plus chemo), and Astra's study of competing BTK inhibitor Calquence in Elevate-TN had a similar design and showed a hazard ratio of 0.1. However, we think the fixed 12-month duration of a Venclexta combination is appealing, and AbbVie is also testing a limited duration Imbruvica/Venclexta combination in CLL (versus Gazyva/chemo) with data expected in 2021. CLL combinations could also evolve to include triple combinations (Astra's phase 3 trial of Calquence/Venclexta/Gazyva against Calquence/Venclexta should have data in 2022). Venclexta is also approved in the 50% of first-line AML patients who are unfit for intense chemo, and we expect strong data to make it the standard of care. The Viale-A showed a strong survival benefit with azicitadine at EHA 2020 (14.7 months versus 9.6 months on azacitadine alone), although Pfizer's Daurismo also saw significant survival benefit in BRIGHT 1003, and Venclexta saw an insignificant survival improvement in confirmatory AML study Viale-C in March 2020. We see potential sales approaching $1 billion in this indication, and studies in RR AML in combination with idasanutlin had efficacy better than either drug alone. In addition, early data in MDS hint that Venclexta combination with azacitadine could improve on azacitadine alone. Phase 3 data from the Bellini study (with Velcade) in 2019 in multiple myeloma showed strong progression-free survival benefit, but higher proportion of deaths in the Venclexta arm limits potential in overall MM market; the Canova trial (with dexamethasone) continues in the 20% of patients with t(11;14) positive disease and should have data in 2021. Early-stage studies are in progress in lymphoma (with Polivy and Gazyva or Rituxan). Overall, we see 70% of Venclexta's 2024 sales coming from CLL, and we see the CLL market growing to $11 billion by 2024.

Product:		Kadcyla
Composition:		biologic (HER2 antibody-drug conjugate)
Economics:		in-house (ImmunoGen ADC technology)
Therapeutic Area:		HER2+ breast cancer
Patents/Generic Threats:		2025+ U.S./EU
2024 Sales:	Morningstar	$1.9 billion
	Consensus	$2.5 billion
Market Model:		—

Kadcyla saw strong data in advanced metastatic HER2-positive breast cancer patients but failed in the first-line metastatic Marianne study to show any benefit over Herceptin plus chemotherapy. However, Katherine data in 2018 showed a 50% reduction in disease recurrence in the adjuvant setting for Kadcyla over Herceptin in patients who had residual disease following neoadjuvant Herceptin treatment (roughly 20% of patients), and we subsequently boosted our Kadcyla estimates (Kadcyla was approved in China based on Katherine data in Jan 2020). Data from the Kaitlin study (Kadcyla and Perjeta versus standard of care Herceptin and Perjeta in the adjuvant setting) are due in 2020 and could be even more impactful. The December 2019 approval of Astra/Daiichi's Enhertu (trastuzumab deruxtecan) in third-line metastatic disease, based on the Destiny-Breast01 study (which showed an impressive ORR of 61% and PFS of more than 16 months despite a median of 6 prior therapies), likely means that Kadcyla will see increased competition as Enhertu expands its label; as of ASCO 2020, Enhertu already had a 30% third-line patient share in the U.S. However, Enhertu's interstitial lung disease/pneumonitis side effect will be monitored, and disease-free survival rates from Roche's portfolio in the adjuvant setting (88% three-year iDFS for the Katherine study and 94% for Perjeta/Herceptin's Aphinity study) set a high bar.

Product:		Lucentis
Composition:		biologic (VEGF-A antibody fragment)
Economics:		Novartis has ex U.S. rights (but Roche has global rights to port delivery system)
Therapeutic Area:		ophthalmology (wet AMD, DME)
Patents/Generic Threats:		2020 U.S./2022 EU (but port delivery 2030+)
2024 Sales:	Morningstar	$1.4 billion (includes port delivery)
	Consensus	$1.2 billion
Market Model:		—

While the Lucentis franchise has lost share to Regeneron and Bayer's dominant therapy Eylea and is also vulnerable to biosimilars (Biogen and Formycon could launch by 2021), Roche's port delivery system should allow the company to refresh IP on this franchise. The phase 2 Ladder study had positive data in 2018, showing that 80% of patients can go at least six months between refills and get similar efficacy as once-monthly Lucentis. The phase 3 Archway trial in wet AMD enrolled rapidly and had positive top-line data in May 2020, showing equivalent efficacy for twice-yearly port delivery to once-monthly Lucentis. While some patients can get away with 12-week dosing with Eylea, we think Lucentis port delivery could be an appealing option for those who still require more frequent dosing. Roche also moved to phase 3 in DME (comparing six-month port delivery to monthly standard Lucentis) in late 2019. Gene therapy could also eventually compete; Regenxbio's AAV gene therapy RGX-314 is entering phase 2b wet AMD and phase 2 DR studies in 2020 (see Regeneron's Eylea for more details on the competitive landscape).

Product:		Alecensa/alectinib
Composition:		small molecule (ALK inhibitor)
Economics:		—
Therapeutic Area:		ALK-positive NSCLC
Patents/Generic Threats:		2031 U.S./EU
2024 Sales:	Morningstar	$1.6 billion
	Consensus	$1.6 billion
Market Model:		—

Overactivation of the ALK protein is the cause of about 5% of cases of NSCLC. While not first to market in the ALK inhibitor class, the head-to-head study Alex against Pfizer's ALK inhibitor Xalkori showed dramatic superiority in 2017, with a 53% reduced risk of disease progression (57% reduction at longer followup in 2018) and an 84% reduced risk of CNS progression (supplemental approval granted by FDA in November 2017). At ASCO 2020, the drug showed impressive five-year survival in the Alex trial at 62.5% versus 45.5% for Xalkori. We think this will be enough to make this the continuing leader in a $2 billion cancer niche, despite the May 2020 approval of Takeda's Alunbrig in the first-line setting, which appears to have similar efficacy (Alta-1L also compared to Xalkori and showed 69% reduction in risk of CNS progression and overall 57% reduced risk of disease progression). Roche is also studying Alecensa in earlier stage (adjuvant) ALK-positive NSCLC patients in the Alina study, with interim data expected in 2022.

Product:		Ocrevus/ocrelizumab
Composition:		biologic (CD20 antibody)
Economics:		assume BIIB royalty reflects 50/50 U.S. split
Therapeutic Area:		RRMS/PPMS
Patents/Generic Threats:		2025+
2024 Sales:	Morningstar	$7.1 billion
	Consensus	$6.7 billion
Market Model:		MS (p.177)

Ocrelizumab's superior efficacy on relapses and disability versus Rebif, strong safety profile, and efficacy in primary progressive disease in phase 3 bode well for uptake, and twice-yearly IV looks convenient; we assume peak sales around $9 billion given the drug's 40% share of new and switch patients in the U.S. The U.S. launch has performed strongly since second quarter 2017, with both primary progressive and relapsing/remitting patients initiating therapy, and patients are switching from a variety of approved MS therapies. Ocrevus gained approval in Europe in January 2018. Novartis/Genmab's ofatumumab generated solid phase 3 data in RRMS in 2019 similar to that of Ocrevus and could compete (PDUFA September 2020), although Ocrevus likely has significant entrenchment with doctors, and existing Ocrevus patients could be hesitant to switch. Subcu administration for ofatumumab could be an advantage, although some patients may prefer to align treatments with twice-yearly doctor visits. That said, Ocrevus infusion time is falling from 3.5 hours to 2 hours with a new dosing schedule in 2020, and Roche is also moving forward with testing a subcu version of Ocrevus.

Product:		Hemlibra/emicizumab/ACE910 (RG6013)
Composition:		biologic (bispecific antibody)
Economics:		—
Therapeutic Area:		hemophilia A, inhibitor and noninhibitor
Patents/Generic Threats:		Beyond 2030
2024 Sales:	Morningstar	$4.4 billion
	Consensus	$4.6 billion
Market Model:		hemophilia (p.173)

This subcu treatment for hemophilia was approved in the $2 billion inhibitor market in November 2017, a setting where it generated an impressive 79% lower bleed risk than other prophylaxis options. We think side effects look manageable and limited to an interaction with Shire's Feiba. Roche had positive data in the broader hemophilia A population ($7 billion market) in November 2017 from Haven 3 (once-weekly dosing and biweekly dosing), and intrapatient comparisons showed superiority to prior factor VIII prophylaxis regimens. Haven-4 (once-monthly dosing) data was strong enough to support the inclusion of once-monthly dosing with expanded noninhibitor approval in October 2018. We think the drug offers a much more convenient regimen with slightly improved efficacy to Shire's Advate, and peak sales could easily surpass $6 billion. BioMarin's gene therapy, Roctavian, could reach the market by the end of 2020, but we expect Roctavian sales to be focused on severe noninhibitor adults and initial uptake to be gradual. That said, if Roctavian durability extends for several years, it does prevent bleeds (40-45% of patients in Roche's HAVEN 3 still had treated bleeds on Hemlibra, although the annualized bleed rate was still quite low around 1). Sanofi's fitusiran (phase 3 data expected in the first half of 2021) could also compete.

Product:		Xofluza (baloxavir marboxil)
Composition:		small molecule (PA endonuclease inh)
Economics:		royalty to Shionogi
Therapeutic Area:		influenza
Patents/Generic Threats:		2031 U.S.
2024 Sales:	Morningstar	$550 million
	Consensus	$500 million
Market Model:		—

Licensed from Shionogi in March 2016, Xofluza was approved in the U.S. in October 2018 in uncomplicated flu, and we expect expansion into high-risk patients, post-exposure prophylaxis, and pediatric settings in 2020-21. Xofluza is differentiated from Roche's now-generic Tamiflu by convenience (one pill total, instead of two pills a day for five days), efficacy (viral shedding for one day instead of three days), and safety (fewer adverse events). We expect the one-pill dosing to be attractive for government stockpiling, and this should boost sales of the drug. That said, we model sales peaking around $1 billion and remaining below Tamiflu's $3.2 billion peak in 2009 (swine flu).

Product:		Polivy (polatuzumab vedotin)
Composition:		Antibody-drug conjugate (CD79b)
Economics:		partnered (Seattle Genetics)
Therapeutic Area:		DLBCL
Patents/Generic Threats:		2030+ U.S./EU
2024 Sales:	Morningstar	$1.1 billion
	Consensus	$1.2 billion
Market Model:		NHL (p.185)

Roche received FDA approval of Polivy with BR (bendamustine and Rituxan) in relapsed/refractory (3L or later) DLBCL in June 2019 based on strong phase 2 data showing a 40% complete response rate for the combination versus only 15% for Rituxan and chemo alone. We think the drug could serve as a strong option for older patients who are ineligible for transplants or CAR-T therapy, and early uptake suggests it could be seen as a viable alternative to CAR-T, given the drug's lower price tag (around $90,000 for the four-month treatment, versus more than $300,000 for CAR-T) and rapid access (off-the-shelf, versus personalized CAR-T). First-line DLBCL study Polarix, which combines Polivy with R-CHOP, should have data in 2020-21; this would significantly expand the market opportunity for Polivy (four times more patients with 1L disease than RR DLBCL) and also help refresh the firm's lymphoma franchise following Rituxan biosimilar headwinds.

Product:		Rozlytrek (entrectinib)
Composition:		small molecule
Economics:		—
Therapeutic Area:		Pan-tumor ROS1 and NTRK fusions
Patents/Generic Threats		2030 U.S./EU
2024 Sales:	Morningstar	$600 million
	Consensus	$450 million
Market Model:		—

Roche received FDA approval of Rozlytrek to treat ROSI1+ lung cancer or NTRK gene fusion positive solid tumors in August 2019, to be used in combination with the FoundationOne companion diagnostic. Roche purchased the drug with Ignyta for $1.7 billion in early 2018. Rozlytrek's 57% response rate in the NTRK-fusion trial did not stack up well with Bayer/Loxo's Vitrakvi's 81% response rate in a similar population, although Roche's trial included many patients with CNS metastases and lacked pediatric patients, potentially weighing on its performance (Roche's data from a separate pediatric study at ASCO 2019 showed a 100% response rate). Vitrakvi was approved in November 2018 in this indication. However, Rozlytrek has a 77% response rate in NSCLC patients with ROS1 fusions (1-2% of NSCLC), giving it a differentiated position in this market, and the subset of patients with brain metastases also performed well (74% response rate). Rozlytrek also launched at a 50% discount to Vitrakvi, at roughly $17,000 per month versus $33,000 per month, but this is in-line with Xalkori's pricing (which is approved for ROS1 patients).

Moat Trend and Product Pipeline

Product:		risdiplam
Composition:		small molecule (SMN2 splicing modifier)
Economics:		partnered (PTC Therapeutics, double-digit royalties)
Therapeutic Area:		spinal muscular atrophy
Launch Year/Probability:		2020/70%
2024 Sales:	Morningstar	$700 million
	Consensus	$1.3 billion
Market Model:		—

Roche is hoping to introduce the first oral treatment for debilitating and deadly neuromuscular disease SMA in 2020 (August 2020 PDUFA) but will compete with Biogen's established intrathecal treatment Spinraza and Novartis' IV gene therapy Zolgensma. While Zolgensma's one-time treatment looks strong and potentially durable (data through five years), Roche's data from Sunfish (type 2 and 3) and Firefish (type 1) studies have been solid, and we believe there could be a place for a safe, oral treatment as an alternative to these other therapies. We expect Roche to gain approval in all types of SMA (all ranges of severity) and to steal share from Spinraza and Zolgensma if priced competitively (Spinraza is $375,000 annually at the maintenance dose). Data from Jewelfish (patients previously treated with Spinraza or Zolgensma) and Rainbowfish (presymptomatic infants) should be available in 2021. Risdiplam could have a particularly advantage over Zolgensma in older patients, as the high dose of Novartis' Strong study (intrathecal administration in type 2 patients) is on a partial clinical hold due to concerning preclinical side effects with this route of administration (inflammation and neuronal cell body degeneration or loss), which could delay Zolgensma's approval in older children (Novartis still hopes to file in 2020). However, Spinraza already treats 10,000 patients out of an estimated total of 45,000 SMA patients, creating some entrenchment. Spinraza data from the presymptomatic Nurture study show that the drug was able to keep patients near normal levels on the CHOP INTEND scale over a two-year period, likely due to earlier treatment, which could also prevent large-scale erosion of sales, and the Devote trial, testing a higher dose of Spinraza, could further improve efficacy (data expected 2022).

Product:		satralizumab
Composition:		biologic (IL-6 antibody)
Economics:		—
Therapeutic Area:		Neuromyelitis optica
Launch Year/Probability:		2020/70%
2024 Sales:	Morningstar	$350 million
	Consensus	$370 million
Market Model:		—

Roche filed for approval in late 2019 in this rare CNS disease, and we think solid efficacy and an excellent safety profile position it for success (August 2020 PDUFA in US, approved as Enspryng in Japan in June 2020). In the phase 3 monotherapy study (Sakurastar), relapse risk reduction was 55% in the overall study, but 74% among AQP4+ patients (anti-AQP4 autoantibodies exist in 70-80% of patients). In Sakurasky (in combination with immunosuppressants), relapse rate reductions were 62% overall and 79% in AQP4+ patients. Monthly subcu dosing looks convenient relative to Soliris' biweekly infusions, although Soliris became the first approved drug for NMOSD in the U.S. in June 2019 (for AQP4+ patients). Soliris could have a lock on AQP4+ patients, given the 94% relapse risk reduction (combo with immunosuppresants) it saw in the Prevent trial, and we see a $2 billion opportunity for Soliris in this market using $500,000 assumed net global pricing. While a rare disease (20,000 in the U.S. and Europe combined), we expect six-figure pricing to make this a more than $500 million opportunity for Roche. Off-label Rituxan remains a significantly more affordable first-line option, but we expect satralizumab to gain first-line use in AQP4- patients. Viela Bio's twice-yearly infused CD-19 antibody inebilizumab (approved as Uplizna in June 2020) could also compete, as it saw solid relapse rate reductions for AQP4+ (77%) and overall (73%) populations.

Product:		etrolizumab
Composition:		Biologic (a4b7/aEb7 antibody)
Economics:		—
Therapeutic Area:		Ulcerative colitis, Crohn's disease
Launch Year/Probability:		2021/70%
2024 Sales:	Morningstar	$700 million
	Consensus	$650 million
Market Model:		UC/crohn's (p. 168)

Roche has been conducting phase 3 trials for etrolizumab for years, but readouts for several of the 8 phase 3 trials in ulcerative colitis and Crohn's disease are scheduled for 2020, likely allowing a filing in UC this year. In 2020, we expect data from TNF-naïve UC studies Hibiscus 1/2 (versus Humira) and Gardenia (versus Remicade), as well as TNF-experienced trials Laurel and Hickory. In 2021, Roche should have data from Bergamot in Crohn's disease. Roche plans to file for approval in 2020, and with 1.3 million moderate to severe patients in the U.S. and EU5, sales could be significant if data compare favorably to Takeda's Entyvio. Roche hopes the dual-action targeting (versus Entyvio's a4b7 focus) could allow it to differentiate itself. Monthly subcu dosing could be a significant advantage over Entyvio, although Takeda is vying to get a bi-weekly subcu formulation to market in 2020 (approved in May 2020 in Europe but delayed in the U.S.) and a potential needle-free injector by 2022.

Product:		RG6042/HTT-ASO
Composition:		RNA oligonucleotide (mHTT)
Economics:		Ionis royalties
Therapeutic Area:		Huntington's disease
Launch Year/Probability:		2021/50%
2024 Sales:	Morningstar	$225 million
	Consensus	$300 million
Market Model:		—

RG6042, part of a collaboration with Ionis, entered a pivotal study in January 2019 and targets toxic mutant huntingtin protein mHTT. There are 30,000 patients in the U.S. with symptomatic Huntington's disease and 200,000 who are at risk of having inherited the disease (61,000 diagnosed in the U.S. and EU5 combined). In a small trial, mHTT protein reductions were 40% at the mean and up to 60% at the max. The current phase 3 study is powered for both bimonthly and triannual dosing; less frequent dosing would be significantly more convenient (intrathecal administration). We expect data from the open label extension of the phase 1/2 study and natural history study in late 2020 or early 2021, which could form the basis of a filing. Phase 3 data should follow in 2022. Recent disappointing efficacy data from Takeda/Wave further solidify Roche/Ionis's lead, although UniQure's gene therapy AMT-130 is beginning to dose patients in a phase 1/2 trial, with first safety data due in 2020 and efficacy data expected in 2021.

Product:		ipatasertib
Composition:		small molecule (AKT)
Economics:		Array BioPharma royalties/milestones
Therapeutic Area:		TNBC, prostate cancer
Launch Year/Probability:		2021/60%
2024 Sales:	Morningstar	$480 million
	Consensus	$650 million
Market Model:		—

We see $1 billion-plus peak sales potential for ipatasertib in breast cancer and prostate cancer; we expect Roche to file this year following phase 3 data from Ipatential-150 (first-line castration-resistant prostate cancer: met endpoint of radiographic PFS in PTEN loss patients in June 2020) and Ipatunity-130 (first-line TNBC and HR-positive breast cancer), allowing regulatory filings this year. Foundation Medicine's broad FoundationOne platform was used to find patients in the phase 2 Lotus trial in TNBC with altered PI3KCA/AKT1/PTEN, showing PFS of nine months for ipatasertib plus chemo in these patients versus 4.9 months for chemo alone. This molecular profile is seen in 35% of the 23,000 new cases of 1L TNBC in the U.S. and EU5 each year and 40% of the 88,000 HR+/HER2- cases. Ipatasertib also has potential in prostate cancer (40-60% with PTEN loss), but a narrower efficacy benefit over standard treatment and side effects in the phase 2 A. Martin study make us cautious. Most recently, promising phase 1b data for the combination of ipatasertib, Tecentriq, and chemo in TNBC (ORR 73%) inspired phase 3 study IPATunity170, which began in November 2019, and the Ipatunity-150 phase 3 study combines ipatasertib with Ibrance in HR+ metastatic breast cancer patients.

Product:		Glofitamab, mosunetuzumab
Composition:		biologic (CD20 bispecifics)
Economics:		—
Therapeutic Area:		blood cancers
Launch Year/Probability:		2022/60%
2024 Sales:	Morningstar	$390 million
	Consensus	$700 million
Market Model:		NHL (p.185)

Roche has two shots on goal with its CD20 bispecifics, with mosunetuzumab looking like the safest CD20 bispecific, and glofitamab as a higher efficacy option, but with more side effects. Mosunetuzumab (from gRED) is being studied in combination with Tecentriq and Polivy, and single-agent data at ASH 2019 showed strong data during dose escalation in aggressive NHL (ORR 37%, CR 19%, 124 patients) and indolent NHL (ORR 63%, CR 43%, 67 patients). Glofitamab (from pRED), which has 2 CD20 binding sites, is in phase 1 trials in combination with Gazyva (follicular lymphoma), Rituxan (DLBCL), or Tecentriq or Polivy (NHL). Monotherapy data at ASH 2018 was promising in late-line aggressive NHL (ORR 54% and CR 27% for 10 mg cohort of 26 patients). An update at EHA 2020 showed ORR/CRs of 46%/31% in aggressive NHL and 65%/52% in indolent NHL for patients on at least 0.6 mg doses, with grade 3 or higher CRS in 3.2% of patients. Glofitamab data at higher 10/16 mg doses in combination with Gazyva at ASH 2019 showed 44% CR in DLBCL and 75% CR in FL, with 7% of patients with grade 3 or higher CRS. Roche has CD20 bispecific competition, however; Regeneron's REGN1979 offered strong data at ASH over the past two years, with recent complete response rates of 71% in follicular lymphoma and 57% in DLBCL (the drug is enrolling a pivotal phase 2 trial). Genmab and AbbVie's GEN3013 (epcoritamab) is in dose expansion in phase 1/2 testing, with data and potential initiation of pivotal programs in 2020.

Product:		faricimab
Composition:		bispecific antibody (Ang-2/VEGF-A)
Economics:		—
Therapeutic Area:		wet AMD, DME
Launch Year/Probability:		2022/50%
2024 Sales:	Morningstar	$225 million
	Consensus	$300 million
Market Model:		—

This is Roche's key ophthalmology development program, beyond Lucentis' port delivery system. Phase 2 data in wet AMD (Stairway study) showed that 65% of patients were capable of maintaining an every-four-month dosing regimen with faricimab, with efficacy similar to monthly Lucentis. In DME (Boulevard study), once-monthly faricimab had better efficacy than once-monthly Lucentis. Faricimab began phase 3 studies Yosemite and Rhine in DME (bimonthly dosing versus Eylea bimonthly) in late 2018 and wet AMD phase 3 studies Tenaya and Lucerne (every-four-month dosing versus Eylea bimonthly) in early 2019, with first filing expected in 2021 given strong trial enrollment (DME data is expected in 2020 and AMD data in 2021). While every-four-month dosing would be an advantage, comparisons with Lucentis are less helpful, so phase 3 comparisons with standard-of-care Eylea will be critical.

Product:		gantenerumab
Composition:		biologic (amyloid beta antibody)
Economics:		partnered (Morphosys)
Therapeutic Area:		Alzheimer's disease
Launch Year/Probability:		2022/20%
2024 Sales:	Morningstar	$350 million
	Consensus	$150 million
Market Model:		Alzheimer's (p.180)

Roche moved to 5x higher gantenerumab doses in a new set of phase 3 studies, graduate 1 and graduate 2, in light of Biogen's phase 1 success with similar antibody aducanumab, despite gantenerumab's earlier phase 3 failure (the Scarlet Road study was stopped for futility in late 2014). Gantenerumab is structurally similar to Biogen's aducanumab and acts primarily on plaque, and Roche had tested higher doses in an open-label extension of the Marguerite Road study. Roche expects interim reads for gantenerumab trials, and we expect first data in 2021 (the two-year trials were fully recruited as of November 2019 pRED day). AC Immune-partnered amyloid antibody crenezumab was also tested at higher doses in phase 3 but failed in CREAD 1 and CREAD 2 (futility) at interim analysis in January 2019 (although a prevention study in genetically at-risk individuals in Colombia continues). While we have removed crenezumab from our model, we think gantenerumab's similarity to aducanumab gives it slightly better prospects, and subcu administration would be a benefit over aducanumab infusion. In addition, the 24-month duration of the study and high-dose availability to APOE4 carriers could make it easier to meet key endpoints than Biogen's Engage and Emerge studies. Roche has a brain shuttle version of gantenerumab in phase 1, which should allow more drug to reach the brain.

Product:		SPK-8011/RG6357
Composition:		Gene therapy
Economics:		—
Therapeutic Area:		Hemophilia A
Launch Year/Probability:		2023/50%
2024 Sales:	Morningstar	$400 million
	Consensus	NA
Market Model:		Hemophilia (p. 173)

Gained as part of the $4.3 billion Spark Therapeutics acquisition which closed in December 2019, SPK-8011 began a lead-in study for phase 3 development at the end of 2018, and updates have been scarce since the Roche acquisition became pending in early 2019. Roche released phase 1/2 data for SPK-8011 at ISTH in July 2020 from five patients in the first dose cohorts, with durable factor VIII expression and a 91% reduction in ABR after more than two years. Roche is still working to optimize dose and control immune responses, with plans to enter phase 3 in 2021 for SPK-8011 (in hemophilia A) and SPK-8016 (in patients with inhibitors). In August 2018, Spark reported a 97% reduction in annualized bleeds in 12 patients treated at the go-forward dose of 2x10^12, with factor VIII expression mean of 30% 12 weeks post-treatment in 5 patients and mean bleed rates reduced 100% in these patients. However, two patients had FVIII declines to less than 5% and were moved to on-demand treatment. An update at ASH 2018 showed continued 100% reduction in bleeds up to 46 weeks after treatment in the 5 high-dose patients who did not have an immune response-associated decline.

Product:		cibisatamab (RG7802)
Composition:		biologic (CEA bi-specific antibody)
Economics:		—
Therapeutic Area:		colorectal cancer, CEA-high cancers
Launch Year/Probability:		2023/30%
2024 Sales:	Morningstar	$240 million
	Consensus	no estimate
Market Model:		—

Roche's CEA-targeting T-cell bispecific, RG7802, produced impressive early-stage data, and we think the drug has peak sales potential north of $1 billion, given its broad potential in colorectal cancer and ability to target roughly 300,000 patients in the U.S. and EU5 who have CEA-high cancer. CEA has long been a biomarker in colorectal cancer, but targeted therapies have failed to see sufficient efficacy. We think RG7802 looks intriguing as the first evidence of a T-cell bispecific working in solid tumors (it uses CrossMAb technology and a differentiated 2:1 format design). Early data for the combo of Tecentriq and RG7802 in refractory colorectal cancer show a disease control rate of 52% and responses in 12% of patients, well above standard treatments, and strong activity (82% disease control) at high doses. We expected updated data in the second half of 2020, after delays due to immunogenicity concerns.

Product:		SRP-9001/RG6356
Composition:		Micro-dystrophin gene therapy
Economics:		Ex U.S. rights (royalties and milestones to Sarepta)
Therapeutic Area:		Duchenne muscular dystrophy (DMD)
Launch Year/Probability:		2023/20%
2024 Sales:	Morningstar	$100 million
	Consensus	$300 million
Market Model:		—

Roche announced the licensing of SRP-9001 from Sarepta in December 2019 for a cost of $750 million upfront and a $400 million equity investment. SRP-9001 delivers a microdystrophin-encoding gene to muscles to allow production of the protein, which muscles need to perform properly. As a potential one-time treatment for a severe rare disease (diagnosed in about 13,000 males in the U.S. and Europe), we expect SRP-9001 would be priced north of $1 million, if approved. Current exon-skipping treatments from Sarepta (Exondys 51 and Vyondys 53) work in a portion of patients were certain genetic mutations, but gene therapy could be more broadly effective. Data from four patients in a small phase 1/2 study showed strong expression of microdystrophin and functional improvements in these patients. A larger, one-year phase 2 study began in late 2018 with data expected in early 2021, and a study using commercial supply is set to start in 2020. Competing gene therapies, Pfizer's PF-06939926 (moving to phase 3 in 2020) and Solid Biosciences' SGT-001 (on clinical hold since November 2019), have serious side effects tied to complement activation, and we think this gives an edge to Sarepta/Roche.

Product:		GDC-0077/RG6114
Composition:		small molecule (PI3K)
Economics:		—
Therapeutic Area:		HER2-/HR+ breast cancer
Launch Year/Probability:		2023/50%
2024 Sales:	Morningstar	$150 million
	Consensus	$120 million
Market Model:		—

Roche pushed this drug into 400-patient late-stage trial Inavo120 in early 2020, comparing the combination with CDK4/6 Ibrance and fulvestrant to these two established treatments alone, in PIK3CA-mutant patients (Roche estimates that 40% of HR+ breast cancer patients are PI3KCA mutants). While Roche has a history of failed PI3K-targeting programs, like pictilisib and taselisib, RG6114 is more selective for PI3K-alpha. Data presented in December 2019 in combination with letrozole and Ibrance showed an overall response rate of 52%. The drug draws comparisons to Novartis' recently approved PI3K-alpha therapy Piqray, but Roche's molecule looks more potent preclinically, and so far, looks easier to combine with CDK 4/6 drugs.

Product:		Tiragolumab/RG6058
Composition:		antibody (TIGIT)
Economics:		—
Therapeutic Area:		Oncology (lung cancer)
Launch Year/Probability:		2023/50%
2024 Sales:	Morningstar	$500 million
	Consensus	$400 million
Market Model:		—

Roche announced in Jan 2020 that it was moving this program ahead to eight pivotal studies, the first with Tecentriq and chemo in first-line SCLC, a second with Tecentriq in PD-L1 positive (TPS>50%) first-line non-small-cell lung cancer, and a third in PD-L1-positive cervical cancer. Earlier-stage studies are ongoing for the combination, and data at ASCO 2020 from Cityscape, a phase 2 study which focuses on tiragolumab and Tecentriq combination therapy in first-line PD-L1-positive NSCLC, produced strong PFS results and similar levels of grade 3 or higher adverse events versus Tecentriq alone. The combination had a hazard ratio of 0.58 (42% reduction in risk of progression or death) in the overall study of patients with a tumor proportion score greater than 1%, but was particularly effective in patients with a TPS>50% (HR=0.30) rather than those with TPS 1-49% (HR=.89). TIGIT is an inhibitory checkpoint receptor on T- cells that is also being pursued by many of Roche's Big Pharma competitors, including Merck (vibostolimab/MK-7684 just entered a phase 2 study with Keytruda and chemo in NSCLC), Bristol (BMS-986207 has been in phase 2 with Opdivo since 2016), and Gilead (via a new collaboration with Arcus, AB154 should have phase 2 data by the end of 2020). Blocking TIGIT is believed to create similar T-cell stimulating activity as blocking CTLA4, although TIGIT and PD-1 in particular could be key to preventing T-cell exhaustion.

Product:		RG6171/GDC-9545
Composition:		small molecule (SERD)
Economics:		—
Therapeutic Area:		HER2-/HR+ breast cancer
Launch Year/Probability:		2023/30%
2024 Sales:	Morningstar	$180 million
	Consensus	no estimate
Market Model:		—

In 2014, Roche paid $725 million upfront to acquire private firm Seragon and its portfolio of selective estrogen receptor degraders. This is the third SERD program Roche has pursued from the Seragon acquisition; it entered development in 2017 and is expected to enter phase 3 in 2020. Roche's dominant breast cancer franchise has historically focused on HER2-positive patients, while SERDs would focus on patients whose tumors are driven by hormone receptors. Patients often become resistant to current treatments, which include generic treatments like estrogen receptor antagonists (fulvestrant and tamoxifen) and aromatase inhibitors (letrozole). Roche sees third-generation RG6171 as potent with minimal safety issues, and if successful it could replace current generics and be used in combination with CDK 4/6 therapies like Pfizer's Ibrance. Roche could face competition from Sanofi's SAR439859, which could be filed in 2021 (phase 2 Ameera-1 data was positive at ASCO 2020, or from Astra's AZD9833 (positive phase 1 data at ASCO 2020).

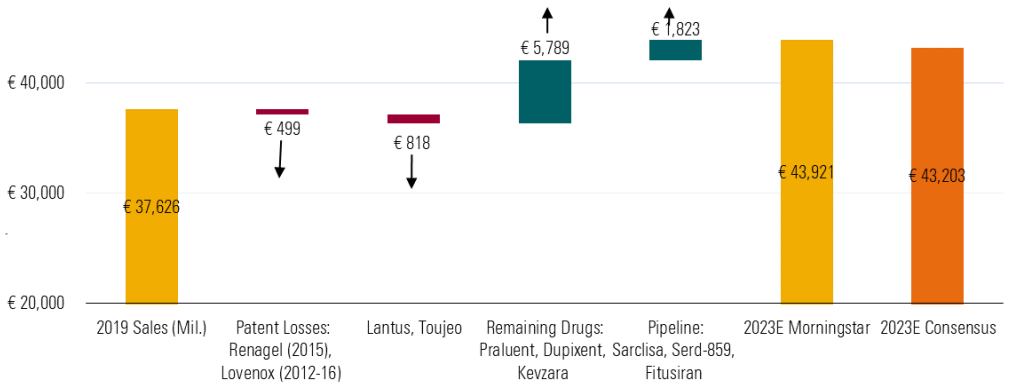
Product:		idasanutlin
Composition:		small molecule (MDM2 antagonist)
Economics:		—
Therapeutic Area:		RR AML
Launch Year/Probability:		2024/0%
2024 Sales:	Morningstar	—
	Consensus	$50 million
Market Model:		—

A Ph Ib study in relapsed/refractory AML showed promising activity as monotherapy (7% CR) and with cytarabine (27% CR). This would be a first-in-class product that could follow use of Venclexta in the 1L AML setting. Although the Mirros study (with cytarabine versus cytarabine alone) successfully passed an interim analysis bar, it failed in first-quarter 2020, and we've removed the drug from our model. The drug is also being studied in combination with Venclexta in RR AML patients ineligible for chemo; phase 2 should begin shortly as phase 1 data at ASH 2019 showed encouraging efficacy greater than either single agent (response rate of 50% and composite complete response of 35% at doses considered for phase 2). A phase 1b/phase 2 first-line fit AML study, with chemo, began in early 2019.

Sanofi SNY

Morningstar Rating™	Fair Value	Price/Fair Value	Uncertainty	Moat	Moat Trend
★★★	$55.00	0.95	Medium	Wide	Stable

Revenue Breakdown EUR Millions



Source: Morningstar, company reports; DrugAnalyst/S&P Cap IQ for consensus.

Lantus Headwinds Remain, but New Drugs and Rare-Disease Platform Mitigate Pressures

Expiring Patents

Lantus (8% of 2019 sales) represents the main headwind for the company, but the complex structure of the drug likely means generic competition will be more limited, probably only from Eli Lilly (2016) and Mylan (2020-21).

Inline Products

Dupixent's leading efficacy data in asthma and atopic dermatitis should drive robust further growth. Sanofi's strong entrenchment in rare disease should continue to support strong pricing power.

Pipeline

The focus on building out the company's rare-disease platform with fitusiran and several other rare-disease drugs should result in both strong pricing power and likely faster ramps as compared with the primary care indications such as diabetes, where the company was historically heavily focused for drug development. Also, a renewed focus on oncology sets up a solid platform for growth over the longer term.

Moat and Product Portfolio

Expiring Patents

Product:		Lantus
Composition:		biologic (insulin glargine)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		2015 U.S./2014 international
2024 Sales	Morningstar	EUR 1,888 million
	Consensus	EUR 1,736 million
Market Model:		insulin (p.176)

Branded and biosimilar competition combined with aggressive PBMs should lead to rapid declines. The complex structure of the drug likely means biosimilar competition from only Eli Lilly (2016), Mylan (2020), and potentially some other manufacturers outside the U.S. Pricing should still fall by over 30% in the U.S., but less in Europe where brand prices are lower.

Product:		Plavix
Composition:		small molecule (antiplatelet)
Economics:		
Therapeutic Area:		blood thinner (heart attack/stroke)
Patents/Generic Threats:		2011 U.S./2009-13 International
2024 Sales	Morningstar	EUR 805 million
	Consensus	EUR 774 million
Market Model:		—

Emerging markets are largely the last remaining sales target of this off-patent drug. China's more aggressive stance on pricing for off-patent drugs should cause declines to accelerate.

Product:		Lovenox
Composition:		small molecule (anticoagulant)
Economics:		—
Therapeutic Area:		deep vein thrombosis
Patents/Generic Threats:		2012 U.S. and Europe/2016 Japan
2024 Sales	Morningstar	EUR 983 million
	Consensus	EUR 1,046 million
Market Model:		—

With the majority of sales generated in Europe, the increasing generic competition in Europe will probably create a drag on the sales. However, the already low price of the product in Europe is likely to slow the declines.

Inline Products

Product:		Aubagio
Composition:		small molecule (pyrimidine synthesis inhibitor)
Economics:		—
Therapeutic Area:		MS
Patents/Generic Threats:		regulatory exclusivity 2023 U.S./2023 OUS
2024 Sales	Morningstar	EUR 508 million
	Consensus	EUR 663 million
Market Model:		MS (p.177)

While lacking the efficacy of other new MS treatments, the oral dosing and relatively clean side effect profile should support continued market gains. Further, recent agreements with generic drugmakers should keep generics off the U.S. market until 2023.

Product:		Toujeo
Composition:		biologic (insulin glargine)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		compound expired, others out to 2034
2024 Sales	Morningstar	EUR 1,189 million
	Consensus	EUR 1,007 million
Market Model:		insulin (p.176)

Parity pricing with Lantus combined with efficacy and dosing benefits should drive market penetration for the drug. However, the deteriorating reimbursement for the drug is concerning following the Eli Lilly Lantus biosimilar launch.

Product:		Praluent
Composition:		biologic (PCSK9)
Economics:		Beginning 2020, U.S. rights REGN, ex U.S. Sanofi (royalty to REGN)
Therapeutic Area:		cholesterol
Patents/Generic Threats:		2029 worldwide
2024 Sales	Morningstar	EUR 370 million
	Consensus	EUR 331 million
Market Model:		—

We think Praluent could benefit the millions of patients whose disease is still uncontrolled with statins, but we've lowered our peak sales estimate to roughly $1 billion given Repatha's stronger launch (partly tied to uncertainty around Praluent's infringement on Repatha patents) and the potential entry of new cholesterol-lowering competitors, such as Novartis/Medicines Company's PCSK9 therapy inclisiran (late 2020 launch expected) and Esperion's cheaper oral ACL inhibitor Nexletol/bempedoic acid (approved Feb 2020). Complete data from Praluent's cardiovascular safety in 2018, matching Amgen's over 15% CV risk reduction and achieving a 22% reduction in risk of death (label expanded in April 2019), does support extended payer coverage after an initial slow ramp. Continued price competition with Amgen has also hit our sales estimates, as new lower list price versions of both Repatha and Praluent have triggered reassessment of PBM contracts. Regeneron locked in an exclusive deal with Express Scripts in 2018 based on cost-effective pricing ranges found in an ICER analysis, although the 2020 preferred formulary includes both Repatha and Praluent.

Product:		Kevzara/Sarilumab
Composition:		biologic (IL-6 inhibitor)
Economics:		45% of profits to Regeneron
Therapeutic Area:		RA
Patents/Generic Threats:		2028 U.S./2029 OUS
2024 Sales	Morningstar	EUR 348 million
	Consensus	EUR 562 million
Market Model:		RA (p.167)

Despite superiority data to Humira, Kevzara is relatively undifferentiated from Roche's blockbuster Actemra, and we've lowered our peak sales estimate to $500 million from $1 billion. Kevzara was approved in May 2017 with a list price set at $39,000 a year for both doses, roughly the same as net prices for TNF drugs Humira and Enbrel, and relatively similar to Actemra's pricing. Kevzara also entered a trial as a treatment for hospitalized patients with COVID-19 in March 2020, but initial results were disappointing, and after failing to see a significant benefit over placebo in severely-ill patients, the trial was subsequently narrowed to the higher 400 mg dose and more advanced, critically ill patients. The trial failed in this setting as well in July 2020; the 400 mg dose produced a positive trend in mechanically ventilated at baseline, but a negative trend in patients not mechanically ventilated at baseline. Regeneron is stopping the 800 mg arm as a result, but an ex US trial continues, with data expected in the third quarter.

Product:		Dupixent/dupilumab
Composition:		biologic (IL-4/13 inhibitor)
Economics:		45% of profits to Regeneron
Therapeutic Area:		atopic dermatitis/asthma
Patents/Generic Threats:		2027-32 U.S./2029-34 OUS
2024 Sales	Morningstar	EUR 6,865 million
	Consensus	EUR 7,147 million
Market Model:		atopic dermatitis (p.164), biologic respiratory (p.171)

We assume $10 billion in peak Dupixent sales, roughly in-line with Sanofi's peak sales goal of more than EUR 10 billion, based on the drug's solid safety and efficacy profile in atopic dermatitis ($4 billion peak) that should withstand incoming competition, superior profile and broader potential in asthma ($4 billion peak) than IL5 antibodies Nucala and Fasenra, as well as expansion into smaller immunology indications over the next two years (total of $1 billion peak) with relatively convenient bi-weekly subcu dosing. Sales are already annualizing north of $3 billion a year, and Dupixent only has a single-digit share of biologics-eligible patients in atopic dermatitis and asthma indications, implying plenty of room to grow.

Sanofi and Regeneron received approval in March/September 2017 in the U.S./Europe in adult atopic dermatitis, and October 2018 in the U.S. in moderate to severe asthma in patients age 12 and up who either have high eosinophil counts (similar to IL-5 labels) or are uncontrolled on oral corticosteroids (differentiated from other biologics). In atopic dermatitis, Regeneron is targeting the 300,000 adults in the U.S. with the most severe disease, gradually expanding approval to smaller but significant populations in adolescents (2019) and pediatric groups of age 6 and up (2020) and six months and up (2022E). In asthma, there are 900,000 moderate to severe patients in the U.S. who are uncontrolled and eligible for biologic treatments, and Dupixent is likely to expand approval to children 6 and up by 2022 (phase 3 data by the end of 2020).

Beyond atopic dermatitis and asthma, Dupixent has numerous other opportunities in the immunology space. Dupixent was approved in June 2019 in patients with nasal polyps (250,000 surgeries in U.S. and EU5 annually). It is also in pivotal studies in eosinophilic esophagitis (phase 2 data was positive in May 2020, phase 3 data 2022E, 160,000 patients in the U.S. alone) and in skin conditions like chronic spontaneous urticaria (hives, 2022E submission), prurigo nodularis (2021E submission), and bullous pemphigoid (2023E submission). We don't model additional indications that could lead to upside, such as the phase 3 COPD program (2 million in U.S. in need of new treatments, but high-risk development area) and mid-stage studies in peanut and grass allergies (peanut allergy trial with Aimmune to have data in 2020).

Product:		Admelog/SAR342434
Composition:		biologic (insulin lispro)
Economics:		—
Therapeutic Area:		diabetes
Patents/Generic Threats:		
2024 Sales	Morningstar	EUR 200 million (in other sales)
	Consensus	EUR 343 million
Market Model:		insulin (p.176)

Admelog/SAR342434 is a biosimilar of Eli Lilly's Humalog, which completed phase 3 in mid-2016. Sanofi launched the drug in the U.S. in early 2018 at close to a 15% price discount to Humalog. However, with Sanofi's decision to move away from focusing on diabetes, we don't see this drug as a core driver for the company.

Product:		Libtayo/Cemiplimab/REGN2810
Composition:		biologic (PD-1)
Economics:		slightly above 45% of profits to Regeneron
Therapeutic Area:		cancer
Patents/Generic Threats:		2035 U.S.
2024 Sales	Morningstar	EUR 346 million
	Consensus	EUR 302 million
Market Model:		immuno-oncology (p.181)

Libtayo is significantly behind other players in the PD-1 antibody market (Bristol and Merck have leading market shares, and PD-L1 therapies from Roche, Astra, and Pfizer have all entered the market), and we're skeptical of Libtayo's ability to differentiate. The drug was approved in the U.S. based on a phase 2 pivotal trial in advanced cutaneous squamous cell carcinoma (second-deadliest skin cancer, high mutation rate) in 2018. We include moderate sales for the drug in this niche indication (where it had gained 48% share of the U.S. market by the end of Q1 2020), where it produces improving complete responses over time (16% as of ASCO 2020), although Merck is expecting approval of Keytruda in this indication (based on data from Keynote-629) in June 2020. Regeneron plans to file in basal cell carcinoma and first-line PDL1-positive NSCLC later in 2020. Data in PD-L1 positive NSCLC patients (PD-L1 on at least half of tumor cells, or 25-30% of diagnoses) showed an ORR of 42% for Libtayo (versus 22% chemo), and the trial was stopped early at an interim survival analysis that showed a 32.4% reduction in risk of death versus chemo. This looks like strong efficacy on par with approved treatments from Roche and Merck, particularly given the fact that a third of patients in the trial enrolled in the last six months (less likely to see significant survival benefit yet) and that all chemotherapy patients are allowed to crossover to the Libtayo arm when they progress (blurring the distinction between the two arms). Regeneron still enrolling a larger phase 3 program with Libtayo in various combinations—a lung cancer trial in combination with chemotherapy should complete enrollment this year (data 2021). We expect Regeneron's potential for differentiation comes from novel combinations. The drug is also in phase 3 in cervical cancer (to file 2021) and in early-stage studies with Sanofi's CD38 antibody Sarclisa, Regeneron'sLAG3 antibody REGN3767 (data 2021), and with internal bispecifics like CD20/CD3 REGN1979 (lymphoma data 2020), CD28/PSMA REGN5678 (prostate cancer data 2024), and MUC16 REGN4018 (ovarian cancer data 2022). Regeneron also entered collaborations to expand its midstage combination therapy trials, combining Libtayo with Inovio's INO-5401 and INO-9012 in brain cancer, SillaJen's Pexa-Vec in kidney cancer, ISA's ISA101b in head and neck cancers, and Vyriad's oncolytic virus Voyager-V1 in multiple tumor types.

Product:		Cablivi/Caplacizumab
Composition:		biologic (anti-vWF nanobody)
Economics:		
Therapeutic Area:		acquired thrombotic thrombocytopenic purpura
Patents/Generic Threats:		
2024 Sales	Morningstar	EUR 427 million
	Consensus	EUR 442 million
Market Model:		—

Approved in Europe in September 2018 and in the U.S. in February 2019 (at a price of $270,000 in the U.S.), the drug treats acquired thrombotic thrombocytopenic purpura. This disease still has a mortality rate of close to 20%. With 7,500 cases a year in developed markets, the targeted group is small, but pricing power is strong. In the phase 3 study Hercules, the drug reduced hospital days by 31%. Sanofi gained the drug through the EUR 3.9 billion acquisition of Ablynx in early 2018.

Moat Trend and Product Pipeline

Product:		Sarclisa/Isatuximab
Composition:		biologic (CD38)
Economics:		—
Therapeutic Area:		blood cancer
Launch Year/Probability:		2020/100%
2024 Sales	Morningstar	EUR 291 million
	Consensus	EUR 494 million
Market Model:		multiple myeloma (p.188)

Isatuximab is an anti-CD38 monoclonal antibody that gained approval in the refractory multiple myeloma setting in the U.S. (Mar. 2020) and Europe (June 2020). In one phase 2 study in highly refractory multiple myeloma patients, the drug helped achieve a PFS benefit of 3.7 months and a median overall survival of 18.6 months. The drug targets a different CD-38 epitope than Johnson & Johnson's Darzalex, which may lead to greater efficacy, but entering the market after Darzalex will be a challenge. A key phase 3 study in combination with Pomalyst and dexamethasone showed a progression free survival improvement of 40%, but the overall survival data hasn't matured enough to show data. Another phase 3 study (IKEMA) was stopped early due to efficacy in the refractory patient population, reducing risk of death by 47%.

Product:		sutimlimab
Composition:		biologic (C1)
Economics:		
Therapeutic Area:		cold agglutinin disease
Launch Year/Probability:		2021/70%
2024 Sales	Morningstar	EUR 173 million
	Consensus	EUR 366 million
Market Model:		

While the drug met its endpoints in phase 3 development, the small number of patients (10,000 in the U.S., Japan and Europe)[26] limits our expectations. The drug gained a priority review from the FDA and should launch in 2021.

Product:		Avalglucosidase alfa
Composition:		biologic enzyme replacement therapy
Economics:		
Therapeutic Area:		Pompe Disease
Launch Year/Probability:		2021/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	
Market Model:		

Avalglucosidase alfa is a next generation treatment option for Pompe disease. Phase 3 data (announced in June 2020) showed the treatment to be more successful than the current standard of care Lumizyme. Avalglucosidase alfa showed a 2.4 point improvement in forced vital capacity (a key respiratory measurement) compared to Lumizyme. Also, avalglucosidase alfa helped patients walk 30 meters farther than Lumizyme patients in a six-minute walk test. Sanofi expect to file the drug in late 2020, but we don't see much incremental gains with the drug as sales will likely come from cannibalizing the firm's entrenched drug Lumizyme.

Product:		fitusiran
Composition:		biologic (RNAi)
Economics:		royalties to Alnylam
Therapeutic Area:		hemophilia
Launch Year/Probability:		2022/50%
2024 Sales	Morningstar	EUR 385 million
	Consensus	EUR 309 million
Market Model:		hemophilia (p.173)

While a clinical hold due to a thrombosis-related patient death in a phase 2 study is concerning, studies are back in progress, and phase 3 data should report out in the first half of 2021, opening up potential approval in 2022. Fitusiran's subcutaneous monthly administration could make it an appealing option for patients, and its mechanism of action (antithrombin) means it could work for patients with hemophilia A or hemophilia B, with or without inhibitors. Also, the annualized bleed rates look better than Roche's leading therapy Hemlibra (1.01 median ABR in patients without inhibitors in phase 2 extension, versus 2.1 for Hemlibra monthly dosing) and dosing for fitusiran looks easier versus Hemlibra (single injection, fixed dosing, no cold chain required).

Product:		SERD-859
Composition:		Small molecule (ER blocker)
Economics:		
Therapeutic Area:		breast cancer
Launch Year/Probability:		2022/50%
2024 Sales	Morningstar	EUR 313 million
	Consensus	NA
Market Model:		

With a strong safety profile, the drug could replace older endocrine therapies that are standard of care in combination with CDK4/6 drugs. The drug has very low rates of grade 3 adverse events, potentially making it better than standard of care fulvestrant (intramuscular injection), and '859 is orally administered, creating better convenience. However, with only phase 1 data available, the outlook is uncertain. The pivotal refractory monotherapy study should report in 2021 followed by pivotal combination studies with CDK4/6 (2024) and PI3Ki (2024).

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Product:		BIV001
Composition:		Biologic/recombinant factor VIII
Economics:		Rights outside of EMEA (where Sobi holds rights)
Therapeutic Area:		hemophilia A
Launch Year/Probability:		2023/50%
2024 Sales	Morningstar	Not meaningful (in other sales)
	Consensus	
Market Model:		hemophilia (p.173)

While late stage data is still needed, the annualized bleed rates for this treatment allow for close to normalized status for patients, but the weekly IV dosing is inconvenient compared to other novel drugs (Roche's Hemlibra, Sanofi's fitusiran) that allow for monthly subcu dosing. We expect phase 3 data in late 2021.

Product:		Venglustat
Composition:		Small molecule (GCS inhibitor)
Economics:		
Therapeutic Area:		rare diseases
Launch Year/Probability:		2024/40%
2024 Sales	Morningstar	EUR 225 million
	Consensus	EUR 125 million
Market Model:		

With early stage data showing potentially best in class oral data in Fabry disease as well as strong data in other lysosomal storage diseases (Gaucher), the drug holds potential, but only limited data is available. Key pivotal data should be available in 2022/2023, setting up potential filings in Gaucher and Fabry disease by 2023. There is the potential to file the drug in 2022 in the rare disease of autosomal dominant polycystic kidney disease based on the high unmet medical need, but only pre-clinical data is available so far in that indication.

Product:		Nirsevimab
Composition:		Antibody
Economics:		Profit share with AstraZeneca/SOBI
Therapeutic Area:		RSV prevention
Launch Year/Probability:		2024/25%
2024 Sales	Morningstar	EUR 50 million
	Consensus	EUR 120 million
Market Model:		

Nirsevimab is a longer-acting antibody than established respiratory syncytial virus (RSV) prophylaxis antibody Synagis, with a broader potential group of infants (including full-term infants) eligible for treatment. Phase 2b data showed nirservimab lowered RSV rates (70%) and RSV-related hospitalizations (78%). While the data looks good, phase 3 data is needed to confirm the efficacy and safety. Phase 3 data in high risk infants is expect in 2021 followed by healthy infants by 2023. Pfizer is also looking to bring an RSV vaccine to the market, likely around the same time.

Product:		SAR442168
Composition:		Small molecule (BTK inhibitor)
Economics:		
Therapeutic Area:		multiple sclerosis
Launch Year/Probability:		2024-25/50%
2024 Sales	Morningstar	NA
	Consensus	
Market Model:		multiple sclerosis (p. 177)

While early stage data looks good, we are still somewhat concerned whether early data showing improvement in surrogate endpoints like brain lesions will translate into strong data for endpoints like reductions in relapse rates and disease progression. Key pivotal data is expected in 2024. The phase 3 studies for the drug include patients across the spectrum (relapsing, primary progressive, and non-relapsing secondary progressive). The drug could compete with Merck KGaA's evobrutinib, another BTK inhibitor entering phase 3 in MS.

Appendix: Market Models

Atopic Dermatitis Market

We think treatments for moderate to severe atopic dermatitis have more than $10 billion in market potential ($6.5 billion by 2024) because of the pervasiveness of the condition, which affects at least 17.8 million people in the U.S., and the limited number of safe treatments for moderate to severe forms of the disease. We expect new biologic treatments to be limited to the severe population, which is close to 1 million in the developed world. While generic corticosteroids and immunosuppressants like cyclosporine are frequently used, both have long-term risk of side effects. For new therapies, pricing varies dramatically by disease severity; Pfizer's topical treatment Eucrisa was launched in 2017 at a price of $580 per 2-ounce tube for milder forms of the disease (the drug failed to see successful uptake), while Sanofi and Regeneron's biologic Dupixent was launched in 2017 at a price of $37,000 per year for patients with moderate to severe disease. We think Incyte's ruxolitinib could be a good option for milder forms of AD. Dupixent's position as market leader in moderate to severe AD looks stable, although competition from oral JAKs (particularly AbbVie's Rinvoq and Pfizer's abrocitinib) and other injectables (like Eli Lilly's lebrikizumab and Galderma's nemolizumab) could slow sales growth.

Outlook for Key Atopic Dermatitis Drugs

Drug (Firm)	Target	2024E Sales ($ Mil)	Delivery	Status	Population	ISGA 0 or 1	EASI	Analysis
Dupixent (SNY/REGN)	IL4/IL13	3,724	300 mg sc, every two weeks	approved (ages 6 and up)	IGA 3 or more (moderate to severe), body surface area >10%	36-39% (9-12% control) at week 16	EASI-75: 44-51% (12-15% control), with TCS: 69% v 23% control, at week 16. EASI 90: 30-36% (7-8% control), with TCS: 40% v 11% control, at week 16	Dupixent is the first approved biologic for atopic dermatitis, and we see peak sales in this indication of $4 billion, as sales could plateau with the launch of oral JAK inhibitors and Lilly's IL13 drug lebrikizumab.
lebrikizumab (LLY)	IL13	900	250 mg sc, every two weeks or monthly	Phase 3 (data H1 2021E)	IGA 3 or more (moderate to severe)	ph 2b: 44.6% (every two weeks) and 34% (every four weeks) had IGA 0 or 1 v 15.3% placebo	Phase 2b EASI-75: 60.6% (every two weeks) 56% (every four weeks) v 24.3% placebo at highest 250 mg dose	Acquired with Dermira in early 2020 for $1.1 billion, lebrikizumab started phase 3 in Oct 2019 as a monotherapy treatment and could launch in 2022. Phase 2b efficacy looks potentially better than Dupixent, and a better side effect profile (less conjunctivitis) as well as the backing of Lilly could be a competitor to Regeneron/Sanofi's blockbuster, particularly if approved for monthly dosing.

Source: Morningstar, company reports.

Outlook for Key Atopic Dermatitis Drugs (Continued)

Drug (Firm)	Target	2024E Sales ($ Mil)	Delivery	Status	Population	ISGA 0 or 1	EASI	Analysis
ruxolitinib (INCY)*	JAK 1/2	300	topical	Phase 3 (positive data H1 2020, to file 2020)	>12 yrs, IGA score 2-3, 3-20% body surface area (mild to moderate)	Ph 3 TRuE-AD1: 50-54% IGA-TS, v 15% placebo Ph 3 TRuE-AD2: 39-51% IGA-TS, v 8% placebo	Ph 3 TRuE-AD1: EASI 75: 56% 0.75% dose, 62% 1.5% dose, 25% placebo Ph 3 TRuE-AD2: EASI 75: 52% 0.75% dose, 62% 1.5% dose, 14% placebo	Incyte released positive phase 3 data for ruxolitinib as a topical treatment for atopic dermatitis in early 2020 in mild/moderate patients at least 12 years of age, and we think this could be a way to avoid some of the JAK-related side effects while still allowing combination treatment with injectables like Dupixent. However, lack of comparison against TCS in phase 3 reduces case for first-line use.
Olumiant (LLY/INCY)	JAK 1/2	76	oral	Phase 3, 2020E filing	moderate to severe (refractory to TCS)	AD4: IGA 21.7% 4mg v 15.5% 2mg v 12.9% 1mg v 9.7% placebo. AD5: vIGA 0 or 1 in 24% 2mg, 13% 2mg, 5% placebo. AD7: 30.6% 4 mg v 23.9% 2mg v 14.7% placebo	Phase 3 BREEZE studies, EASI 75: AD1: 24.8% 4mg v 18.7% 2mg v 8.8% placebo AD2: 21.1% 4mg v 17.9% 2mg v 6.1% pbo AD4 (post-cyclosporine) with TCS: 31.5% 4 mg v 27.6% 2mg v 22.6% 1mg v 17.2% pbo AD5 (mono): 29.5% 2mg v 12.9% 1mg v 8.2% pbo AD7 w TCS: 47.7% 4mg v 43.1% 2mg v 22.9% pbo	Olumiant had mixed data in phase 2 studies, with significant results only at the highest dose tested. Phase 3 data was positive, but not as strong as Dupixent, and one patient had a pulmonary embolism in the AD-7 trial.
Rinvoq (upadacitinib) (ABBV)	JAK1	800	oral	Phase 3, 2021E approval	moderate to severe (refractory to TCS or contra-indicated)	Phase 3 Measure Up 1: IGA 0 or 1 at 16 weeks: 48% 15 mg, 62% 30mg, 8% placebo	In Phase 3 Measure Up 1: EASI 75 at week 16: 80% at 30mg and 70% at 15mg v 16% placebo	With no CV SAEs in the first phase 3 study in June 2020 (serious infections 0.7% v 0% placebo), very strong efficacy data that exceeds Dupixent's, and oral dosing, we expect Rinvoq could be a formidable competitor. We expect filing in H2 2020, and a H2H study v Dupixent should have data in 1Q 2021.
abrocitinib (PFE)	JAK1	700	oral	Phase 3, 2020E filing	moderate to severe (TCS inadequate or contraindicated)	JADE-MONO-1: IGA response rate 43.8% 200 mg, 23.7% 100 mg (7.9% placebo) JADE-MONO-2: IGA response rate 38.1% 200mg, 28.4% 100mg (9.1% placebo) JADE COMPARE: Dupixent, and 100mg/200mg doses of abrocitinib, superior to placebo	EASI 75 at week 12: JADE MONO-1: 62.7% 200mg v 39.7% 100mg (11.8% placebo) JADE MONO-2: 61% 200mg v 44.5% 100 mg (10.4% placebo)	Abrocitinib's efficacy data so far appear better than Dupixent, although Dupixent's strong safety profile makes it tough to displace, and Rinvoq looks like the JAK to beat. Phase 3 data were solid, but introduced concerns about safety beyond the typical cardio JAK AEs (higher levels of nausea and headache, one SAE for IBD in MONO-1, lower platelet counts and increased infections in MONO-2). H2H data against Dupixent in March 2020 from Jade-Compare showed the 200mg dose was significantly better at reducing itch by week 2 than Dupixent.
ZPL389 (NVS)	H4 receptor antagonist	NM	oral	Phase 2 (data 2020-22)	IGA 3 or more (moderate to severe)		reduced by 50% (27% placebo) at 8 weeks	While Novartis's MOR106 (IL-17C) failed in 2019, ZPL389 still has first in class potential as an oral H4 receptor antagonist, and a good early-stage data set suggest ZPL389 is a contender in the class (two phase 2 studies in progress)

EASI: eczema area and severity index, EASI-50, 50% improvement in EASI score; EASI-75, 75% improvement in EASI score; EASI-90, 90% improvement in EASI score.
ISGA: investigator's static global assessment score: clear (0), almost clear (1), mild (2), moderate (3), severe (4), IGA: investigator's global assessment, IGA: investigator's global assessment, TCS: topical corticosteroids.
*Ruxolitinib sales estimate also includes sales in vitiligo
Pipeline also includes IL31 nemolizumab (Galderma started phase 3 in October 2019, Ph 2b EASI-75 49% versus 19% placebo for patients on steroids at 24 weeks), JT/Torii's delgocitinib, Sienna's SNA-125.
Source: Morningstar, company reports.

Psoriasis Market

Major advancements to existing drugs on both efficacy and safety should significantly expand the psoriasis and psoriatic arthritis markets. Phase II data from Bristol's BMS-986165 opens the mild/moderate psoriasis market up more with this highly effective and safe new drug. While the TNF drugs will increasingly lose share to biosimilars, we expect the IL17 and IL 23 drugs to displace TNF drugs because of superior efficacy. We expect IL-23 to gain the most share over the long run in psoriasis based on superior long-term efficacy.

Outlook for Key Psoriasis Drugs

Drug	Target	Sales 2024E ($B)	Dose (After Loading)	Status	Side Effects	Baseline PASI Score	PASI 75	Comment
Remicade - JNJ	TNF	0.1	Every 8wks IV	Approved	Tuberculosis, infection, lymphoma	18-21	75-88% at 10wks	Older entrenched drug
Humira - ABBV	TNF	1.5	Every 2wks SC	Approved	Tuberculosis, infection	19	71% at 16wks	Older entrenched drug
Enbrel - AMGN/PFE	TNF	0.8	Weekly SC	Approved	Infection, Malignancies	15-17	47% at 12wks	Older entrenched drug
Stelara - JNJ	IL12 and IL23	4.7	Every 12wks SC	Approved	No Black Box	17-18	66-76% at 12wks	Better than Enbrel in ACCEPT study
Otezla - AMGN	PDE4 inhibitor	3	Twice Daily, Oral	Approved	No Black Box	25	29-33% at 16wks	Oral drug could target less severe group
Cosentyx - NVS	IL-17A	3.7	Every 4wks SC	Approved	No Black Box	20	67-87% at 12wks	Data superiority to Enbrel and Stelara, approved for PA, AS
Taltz - LLY	IL-17A	3.2	Every 4wks SC	Approved	No Black Box	17-18	87-90% at 12wks	PASI 100 hit with 31-41% vs. 5-7% for Enbrel, Outperformed Tremfya on PASI 100 (41% vs. 25%) in short term
Siliq - VRX/AZN/LEO	IL-17 receptor	0.5	Every 2wks SC	Approved	Suicide Concerns	19-20	60-86% at 12 wks	Concerns about suicidal side effects, but superior to Stelara, PASI 100 of 24-44%
Tremfya - JNJ	IL-23	2.8	Every 8wks SC	Approved	No Black Box	18	83-91% at 16wks	VOYAGE 1 outperformed Humira on PASI 90 (80% vs. 53%) at 16wk, Eclipse data showed 85% of patients at PASI 90 by week 48 vs. 70% for Cosentyx
Ilumya - Sun	IL-23	0.5	Every 12wks, SC	Approved Apr. 2018	No Black Box		64% at 12wk	Better than Enbrel
Skyrizi/Risankizumab - ABBV	IL-23	2.8	Every 12wks, SC	Filed 2Q18	Likely no Black Box Warning	--	75% PASI 90 at 16wk	Outperformed Stelara on PASI 90 in Phase II (77% vs. 40%), Outperformed Cosentyx on PASI 90 (87% vs. 57%)
Following drugs are key late-stage drugs								
Mirikizumab - LLY	IL-23	0.7		Phase III	Likely no Black Box Warning	--	75-80% PASI 90 at 48wk	Phase III data expected in 2020
BMS-986165 - BMY	TYK2	0.5	Daily/Twice Daily	Phase III	Likely no Black Box Warning	19-/+6	75% PASI 75 at 12wk	Data is in biologic refractory
bimekizumab - UCB	IL-17A/F	1.1	--	Phase III	Likely no Black Box Warning	--	79% PASI90 at 12 wks	Slightly different mechanism might offset late entry to market, outperformed Humira in Be Sure study, to be filed in mid-2020

Source: Morningstar, company reports.

Rheumatoid Arthritis Market

We expect relatively slight growth in the rheumatoid arthritis class as biosimilar versions of TNF biologics offset new drug launches. Remicade's IV administration has made it a less popular option in RA, so the launch of biosimilar Remicade has less impact on our RA forecast. However, we expect sales of TNFs to begin to drop significantly in 2023 with the likely launches of biosimilar Humira versions in the United States. Biosimilar Remicade (U.S. and Europe) and Enbrel (Europe) are already launching. The next-generation JAK inhibitors are poised for strong growth as they are likely to offer better safety profiles than Xeljanz and better efficacy than the TNFs.

Overview of Key Rheumatoid Arthritis Drugs

Product (Company)	Mechanism of Action	2024E Sales ($B)	Status/ Approval Date	RA Dosing	Black Box	ACR 70	Population
Methotrexate (Several)		-	~1980s	Oral weekly	Toxic Reactions	14-27% at 6 to 12 months 0-10% at 6 to 12 months	Methotrexate Naïve Methotrexate Experienced
Enbrel (Amgen/Pfizer)	TNF alpha	1.6	1998	Weekly Injection	Infection, Malignancies	15% at 6 month (plus MTX)	Methotrexate/DMARD Experienced
Remicade (JNJ/Merck)	TNF alpha	0.8	1999	IV injection every 8wks	Tuberculosis, infection, lymphoma	11-26% at week 54 (plus MTX)	Methotrexate Experienced
Humira (Abbott)	TNF alpha	3.1	2002	Bi-Weekly Injection	Tuberculosis, infection	23% at 12 months (plus MTX)	Methotrexate Experienced
Cimzia (UCB)	TNF alpha	1	2009	Bi-Weekly Injection	Tuberculosis, infection, lymphoma	21% at 52 weeks (plus MTX)	Methotrexate Experienced
Simponi (JNJ/Merck)	TNF alpha	1.3	2009	Monthly Injection	Tuberculosis, infection, lymphoma	20% at week 24 (plus MTX) 9% at week 24 (plus MTX)	Methotrexate Experienced anti-TNF Experienced
Orencia (Bristol)	CTLA4	1.5	2005	Weekly Injection	Relatively Clean	29% at 12 months (plus MTX) 10% at 6 months (plus DMARD	Methotrexate Experienced anti-TNF Experienced
Rituxan (Roche/Biogen)	CD20	0.9	2006	IV injection twice a year	Fatal Infusion reaction, TLS, PML	12% at week 24	anti-TNF Experienced
Actemra (Roche)	IL6r	2.2	2010	Weekly/Bi-Weekly injection	Tuberculosis, infection	16-20% at week 52 (plus MTX) 5-12% at week 24 (plus MTX)	Methotrexate Experienced anti-TNF Experienced
Kevzara/Sarilumab (SNY/RGEN)	IL6r	0.4	2017	Bi-Weekly injection	Similar to Actemra and Humira	20-25% at week 24 (plus MTX) 15-20% at week 24 (plus MTX)	MOBILITY - Methotrexate Experienced TARGET - TNF Experienced
Xeljanz (Pfizer)	JAK 1/3	2.2	2012 US/	Oral-Once Daily	Infection, lymphoma	22% at 6 months 14% at 6 months (plus MTX) 16% at 6 months	Methotrexate/Biologic Experienced Methotrexate Experienced TNF Experienced
Olumiant (Eli Lilly/Incyte)	JAK 1/2	1.5	2018 US/ 2017OUS	Oral-Once Daily	Infection/ VTE/ cancer risk	30% at week 24 (plus MTX) 24-25% at week 24 (plus DMARD) 13-17% at week 24	BEAM- Methotrexate Experienced BUILD- DMARD Experienced BEACON- TNF Experienced
Filgotinib (Gilead/GLPG)	JAK 1	1.2	Filed in late	Oral-Once or Twice Daily	Testicular safety	21-39% at week 24 (plus MTX) 25-26% at week 24 29-36% at week 24 (plus MTX), 20-32% at week 24 40-44% at week 24 (plus (MTX)	DARWIN1 - Methotrexate Experienced (Phase II) DARWIN2 - Methotrexate Experienced (Phase II) FINCH1 - Methrotrexate Experienced (Phase III) did not statistically beat Humira on ACR scores FINCH2 - Biologic Experienced (Phase III) FINCH3- Naïve patients (Phase III)
Rinvoq/Upadacitinib (AbbVie)	JAK 1	1.8	2019	Oral-Once Daily	Relatively Clean	22-24% at week 12 (plus MTX) 27% at week 12 (plus MTX) 21.5% at week 12 (plus DAMRD) 25% at week 12 (plus MTX) 32-37% at week 12 23-33% at week 14	SELECT-BEYOND - Biologic Experienced (Phase III) SELECT-NEXT - Methrotrexate Experienced (Phase III) SELECT-CHOICE statiscially best Orencia on ACR 70 SELECT-COMPARE-Methrotrexate Experienced (Phase III) statistically beat Humira at approved dose SELECT-EARLY Methrotrexate Naive (Phase III) SELECT-MONOTHERAPY Methrotrexate Experienced (Phase III)

*MTSS is calculated using the modified Sharp/van der Heijde method and is based on the combined radiographic scores of joint damage in the hands and feet.
Source: Morningstar, company reports.

Crohn's Disease and Ulcerative Colitis Markets

We expect mid-single-digit growth as declines in sales of older TNF products—which are led by Humira and Remicade and together account for over half of today's global IBD market for biologics and novel oral treatments—are more than offset by growing sales for biologics Stelara and Entyvio and the expected launches of several new classes of oral drugs. We think this dynamic will allow for stable global pricing for patented treatments, while biosimilars should create headwinds.

Short-Term Efficacy in Crohn's Disease Trials

Drug	2024E Sales ($B)	n	Response	Placebo (P-Value	Remission	Placebo (P-Value)	Population
Remicade (JNJ/MRK) at week 4	0.35	108	0.81	16% (P<0.001)	0.48	0.04	Inadequate response to conventional therapies
Humira (ABBV) at week 4	0.8	150	58%	34% (P<0.01)	36%	12% (P<0.001)	TNF Naïve
Humira at week 4		325	52%	34% (P<0.01)	21%	7% (P<0.001)	Intolerant to Remicade
Cimzia* (UCB) at week 6	0.4	659	35%*	27% (P<0.05)	0.22	27% **(P>0.05)**	Moderate/Severe
Tysabri (BIIB) at week 8	1	509	56%	40%	32%	21%	Moderate/Severe
Entyvio* (Takeda) at week 6	1.6	368	31%*	26% **(P=0.23)**	0.15	7% (P=0.02)	Moderate/Severe with 58% TNF Failures
Stelara* (JNJ) at week 6	2.5	628	52-56%	29% (P<0.001)	31-40%	20% (P=0.009)	Refractory, but TNF Naïve
Stelara* (JNJ) at week 6		741	34%*	22% (P<0.003)	16-21%	7% (P<0.003)	Moderate/Severe with TNF Failure/Intolerance
Risankizumab* (ABBV) at week 12	0.9	Phase II n=121	37-42%	0.21	24-37%	0.15	Moderate/Severe
filgotinib (GILD/GLPG) at week 10	0.2	Phase II n=174	60%*	41% (p<0.05)	48%	23% (P=0.0067)	Moderate (CDAI 220-450 at baseline, mean 293), 58% TNF failures
Rinvoq/Upadacitinib (ABBV) wk 52	0.1	Phase II n=94	42-71%		16-26%	0% (P<0.01)	Biologic refractory
Zeposia/Ozanimod (CELG) at week 17	0.2	Phase II n=69	66%*		46%		Moderate/Severe

*Response required 100-point or greater reduction in CDAI score, all others required 70-point reductions.
Source: Morningstar, company reports.

Long-Term Maintenance in Crohn's Disease

Drug	Dose after Loading	n	Remission	Placebo (P-Value)	Black Box
Remicade at 30 weeks (5/10mg)	Every 8wk IV	311	39% 5mg. 46% 10mg.	11% (P=0.022 5mg., 0.001 10mg.)	Yes
Humira at 26 weeks	Every 2wk SC	342	40%	17% (P<0.001)	Yes
Cimzia at 26 weeks	Every 4wk SC	659	0.29	18% (P<0.05)	Yes
Tysabri at month 9	Every 4wk IV	331	45%	26% (P<0.005)	Yes
Entyvio at 52 weeks	Every 8wk IV	307	0.39	22% (P=0.001)	No
Stelara at 22 weeks	Every 8 or 12wk SC	388	49-53%	36% (P=0.04)	No

Source: Morningstar, company reports.

Ulcerative Colitis Treatments

Marketed Drug	2024E Sales ($B)	Dosing after Loading	N	Clinical Remission	Placebo Effect (P-value)	Sustained Clinical Remission	Placebo Effect (P-value)	Patient Population	Black Box Warnings
Remicade - JNJ	0.35	Every 8wk IV	728	28-39%	6-15% (P<0.01)	34-35%	17% (P<0.01)	Biologic naïve	Yes
Simponi - JNJ	0.3	Every 4wk SC	504	0.18	6% (P<0.0001)	0.5	31% (P<0.001)	Biologic naïve	Yes
Humira - ABBV	0.75	Every 2wk SC	754	17-19%	9% (P<0.05)	0.173	8.5% (P<0.05)	23% had used TNF	Yes
Xeljanz - PFE	0.2	2x Daily Oral	1139	12-26%	0-16% (P<0.01)	34-41%	11% (P<0.001)	53-58% TNF failed	Yes
Stelara - JNJ	2.5	Every 8wk SC	961	0.14	4% (P<0.001)	0.41	18% (<0.001)	Biologic Failure	No
		Every 8wk SC	523	0.24	9% (P<0.001)	0.49	36% (P<0.001)	Non-biologic Failure	
Entyvio - Takeda	1.6	Every 8wk IV	374	0.17	5% (P=0.001)	0.42	16% (P<0.001)	41% failed TNF	No
Note: Zeposia - BMY: True North Study met endpoints (p-value < 0.0001 for results for induction of clinical remission at Week 10 and in maintenance at Week 52) with details expected in 2020.									
Pipeline									
ozanimod - BMY	0.2	1x Daily Oral	197	0.16	6% (P=.0482)	0.21	6% (P=.0108)	receiving orals/steroids	NA
SHP647 - Takeda		Every 2wk SC	357	0.167	2.7% (P<0.05)			43% TNF naïve	NA
etrolizumab - RHHBY	0.7	Every 4wk SC	120	10.3-20.5%	0			about 63% failed TNF	NA
Rinvoq- ABBV	0.1	7.5-45mg daily Oral	204	9-20%	0	No data		Refractory/some biologic failure	
filgotinib - GILD	0.2	1x Daily Oral	659	0.261	15.3% (p=.0157)	0.372	11.2% (p<.0001)	biologic naïve	NA
filgotinib - GILD		1x Daily Oral	689	0.115	4.2% (p=.0103)	0.372	11.2% (p<.0001)	biologic experienced	NA

Clinical remission defined as a Mayo score <2 points, no individual subscore >1, patient population: moderate to severe/Mayo scores 6-12 (biologic naive).
Source: Morningstar, company reports.

Nonbiologic Respiratory Market

The heavy outlicensing of key drugs shows the pricing challenges of the market, but the introduction of LAMA combinations, starting in 2013, brought a wave of innovation into a relatively dormant therapeutic area. However, the gains in both efficacy and convenience (several new drugs are dosed daily instead of twice daily) haven't given the payers enough advancement to allow for pricing power, and several new drugs are priced at or below historical prices. We expect this trend of pricing-power weakening to continue, but volume growth should help offset the pricing headwind as both aging developed markets and growing wealth in emerging markets should drive demand in asthma and COPD. The U.S. generic launch of Advair will likely further hurt pricing power in this group. We expect some pricing stabilization with the triples (LABA+LAMA+ICS) given the strong efficacy and more limited competition.

Outlook for Key Nonbiologic Respiratory Drugs

Drug	2019 Sales ($B)	2024E Sales ($B)	Type	Indication	Approval Year	Dosing	Comment
Advair - GSK	2.2	1.1	CS + LABA	Asthma/COPD	2000	Inhaled 2x daily	U.S. generic launched in 2019
Symbicort - AZN	2.5	1.7	CS + LABA	Asthma/COPD	2006	Inhaled 2x daily	Increasing rebates to gain market share
Breo/Relvar - GSK	1.2	1.5	CS + LABA	Asthma/COPD	2013	Inhaled 1x daily	
Dulera - MRK	0.3	0.2	CS + LABA	Asthma	2010	Inhaled 2x daily	
QMF149 - NVS*	0.8	0.3	CS + LABA	Asthma	Phase III	Inhaled 1x daily	
Spiriva - BIIB	2.1	1.4	LAMA	COPD	2004	Inhaled 1x daily	2014 U.S. patent extension to 2018
Seebri - NVS*	0.1	0.2	LAMA	COPD	2012	Inhaled 1x daily	Similar to Spiriva
Incruse - GSK	0.3	0.3	LAMA	CODP	2014	Inhaled 1x daily	Superior to Spiriva
Tudorza/Eklira - AZN^	0.1	0.2	LAMA	COPD	2012	Inhaled 2x daily	Similar profile to older drugs
PT001 - AZN	0.0	0.3	LAMA	COPD	Late-stage	Inhaled 2x daily	Provided in pressurized inhaler for elderly
Anoro - GSK	0.6	0.7	LABA + LAMA	COPD	2013	Inhaled 1x daily	Superior to Spiriva
Stiolto Respimat - BI		0.5	LABA + LAMA	COPD	2015	Inhaled 1x daily	
Ultibro (Arcapta+Seebri)- NVS*	0.4	0.6	LABA + LAMA	COPD	2013-15	Inhaled 1x daily	US is only 2x daily, Outperformed Advair
Bevespi/PT003 - AZN	0.0	0.4	LABA + LAMA	COPD	2016 in US	Inhaled 2x daily	Provided in pressurized inhaler for elderly, not as good as Anoro in COPD
Duaklir - AZN^	0.1	0.3	LABA + LAMA	COPD	2014 in EU, ROW 2018E	Inhaled 2x daily	
Trelegy - GSK	0.7	2.4	LABA + LAMA +ICS	Asthma/COPD	2017	Inhaled 1x daily	Outperformed Symbicort
PT010 - AZN	0.0	0.3	LABA + LAMA +ICS	Asthma/COPD	Filing in 2019E	Inhaled 2x daily	Provided in pressurized inhaler for elderly
QVM149 - NVS*	0.0	0.3	LABA + LAMA +ICS	Asthma	Phase III	Inhaled 1x daily	
Daliresp - AZN	0.2	0.2	PDE4 inh.	COPD	2011	Oral 1x daily	More severe patient group

*Outlicensed in the U.S. to Sunovion and also includes Onbrez/Arcapta (LABA). ^Outlicensed in the U.S. to Circassia.
Source: Morningstar, company reports.

Biologic Respiratory Market

We think the nearly $6 billion market for biologics to treat severe asthma could grow to $10 billion by 2024 as novel therapies launch with better efficacy, broader efficacy, and enhanced convenience. Several IL5 therapies are now approved, and we expect Dupixent's (IL4/IL13) recent approval and broad label will allow it to dominate the IL5s. In the long run, Astra/Amgen's tezepelumab could compete (data late 2020E). Up to 3 million people worldwide have severe asthma that is not controlled with standard asthma inhalers and oral corticosteroids. Drugs are differentiated based on whether they work in different types of patients, as inflammation can be driven by not only blood eosinophils, but also by IL-4, IL-13, or non-T2 pathways. Roughly two thirds of patients with severe asthma are T2-high (greater than 150 cells/mcL--50% are greater than 300 cells/ucL).

Outlook for Key Biologic Respiratory Drugs

Drug (Firm)	2024 Sales ($ Mil)	Type	Dosing	Population	Exacerbation reduction rate	Analysis
Xolair (Roche/Novartis)	2,300	IgE	sc every 2 wks	moderate to severe allergic asthma, age 6 and up, not controlled by corticosteroids	25% relative reduction rate	The original biologic treatment for severe asthma continues to perform well in asthma and hives, but new competition appears to have stronger efficacy (including a Glaxo switch study showing a 64% drop in exacerbations requiring oral steroids in patients switching from Xolair to Nucala).
Dupixent/dupilumab (Sanofi/Regeneron)	3,300*	IL4/IL13	sc every 2 wks	moderate to severe asthma, 12 and up, either oral corticosteroid dependent or high eosinophil counts	QUEST: 300 mg Q2W: reduce severe asthma attacks 60% in patients with 150 eosinophils/mcL or greater and 67% in 300 cells/mcL or greater (no significant impact below 150). VENTURE (with OCS) 300 mg Q2W: reduce severe attacks 59% overall, 71% in >300 eosinophils/mcL	Following Dupixent's 2017 launch in atopic dermatitis, Sanofi and Regeneron launched Dupixent in asthma in late 2018. The FDA's label for Dupixent in asthma covers a broader range of patients than new IL5 antibodies targeted at high eosinophil counts.
Nucala/mepolizumab (Glaxo)	1,476	IL5	sc every 4 wks	severe asthma, high eosinophil counts	47-53% reduction	Nucala was the first-mover in the IL5 field, but Astra's Fasenra should limit growth. However, an indirect comparison to data from Cinqair and Fasenra matched by eosinophil count showed a 34-45% exacerbation reduction for patients using Nucala.
Cinqair/reslizumab (Teva)	NM	IL5	IV every 4 wks	severe asthma, high eosinophil counts	50-59% reduction	Approved in early 2016, Cinqair is competing in a crowded market, and IV administration could make it difficult to gain traction against first-mover Nucala (subcu administration trials failed on efficacy in early 2018).
Fasenra/benralizumab (Astra)	1,827	IL5 receptor	sc every 8 wks	severe asthma, high eosinophil counts	ZONDA: 70% reduction (severe asthma, high-dose ICS/LADA and OCS) CALIMA: 36% reduction (Q4W) and 28% reduction (Q8W) (severe and uncontrolled on ICS/LABA), SIROCCO: 45% reduction (Q4W) and 51% reduction (Q8W) (severe and uncontrolled on ICS/LABA)	Fasenra was FDA approved in November 2017. Targeting the receptor (causing eosinophil apoptosis) leads to faster efficacy than targeting IL5 molecule (passive reduction in eosinophils), so this is the only biologic with dramatic impact on eosinophils within 24 hours. Prefilled syringe is more convenient than Nucala, Cinqair, and Xolair (which require constiution at the doctor's office). 8-week dosing (after first three doses) is differentiated.
tezepelumab (Amgen/Astra)	1,100**	TSLP	sc every 2 or 4 wks	severe uncontrolled asthma, despite inhaled corticosteroids/LABA	PATHWAY (Ph 2): 61-71% reduction (independent of baseline eosinophilic count)	Tezepelumab targets a master switch that controls multiple inflammatory pathways, and phase 2 data is still early, but could make it the most effective biologic in severe asthma, across all eosinophil counts. Phase 3 data in severe uncontrolled asthma and steroid-dependent asthma is expected late 2020. Amgen books sales--we assume a 60% probability of approval in 2021.

*Morningstar estimate of Dupixent-asthma only. **Amgen to book global sales, split economics 60/40 with Astra.
Source: Morningstar, company reports.

Atrial Fibrillation Market

The maturing of the factor Xa drugs means less market potential remains for both Xarelto (Bayer/JNJ) and Eliquis (Bristol/Pfizer) as the old anticoagulant warfarin has lost significant share of the market with around 25% market share left in the U.S. Also, Xarelto is working to expand its label into several new indications, including PCI, PAD, and CAD. Bristol/Pfizer are not running any new Eliquis studies but independent groups are looking at the drug in several new areas.

Outlook for Key Atrial Fibrillation Drugs

Drug (company)	2019 Sales ($B)	2024E Sales ($B)	Dosing	Prevention of Stroke	Bleeding	Mortality	Expected Peak Market Share
Warfarin (comparator)	--	--					15%, down from 25% in 2019
Eliquis (BMY/PFE)*	4.2	6.6	2x daily	significantly superior efficacy on stroke prevention (1.27% vs. 1.6%, p<0.001)	significantly superior reduction in bleeding (2.1% vs. 3.1% p<0.001)	11% reduction p=0.47	50%, up from 45% in 2019
Pradaxa (BI)	1.6	1.6	2x daily	significantly superior at 150mg (1.1% vs. 1.7% p<0.001) non-inferior at 110mg.	similar bleeding (3.1 vs 3.4%) at 150 mg and (2.7% vs. 3.4%) for the 110mg.	trend to 12% lower at 150 mg. p=0.51	5%, flat
Xarelto (BAY/JNJ)	4.4 (Bayer), 2.3 (JNJ)	4.0 (Bayer), 3.5 (JNJ)	1x daily	non-inferior on stroke prevention (2.1% vs. 2.4%)	non-inferior on bleeding (14.9% vs. 14.5%)	trend to lower at 8%	30%, up from 25% in 2019

Source: Morningstar, company reports.

Hemophilia Market

The overall hemophilia market stands at more than $10 billion, and we expect sales of the biggest products (excluding plasma-derived replacement therapy) to grow to $13 billion in 2024, largely because of recent more convenient treatment options and the first launches of gene therapies. One of the more significant disruptors is Roche's Hemlibra; the drug was approved in the $2 billion inhibitor market in late 2017, where Takeda's Feiba and Novo Nordisk's NovoSeven are in decline, and received FDA approval in the broader noninhibitor market in October 2018, where it now competes with standards such as Takeda's Advate and Sanofi/Sobi's Eloctate. We see peak Hemlibra sales reaching $6 billion. In the smaller hemophilia B market, BeneFix's dominance is being eroded as more long-acting products reach the market, including Sanofi/Sobi's Alprolix and CSL's Idelvion. In gene therapy, BioMarin's Roctavian (to launch 2020) in hemophilia A and products from uniQure/CSL and Pfizer/Spark (to launch 2022E) in hemophilia B lead the way, although there is still significant uncertainty around duration of "cures."

Outlook for Key Hemophilia Products: Gene Therapy

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Hemophilia subtype	Administration	Comments
Roctavian (BMRN)	-	1,100	Hem A	once (curative)	BioMarin has the most advanced hemophilia A gene therapy program. Roctavian had encouraging four-year phase 1/2 data, with FVIII declines slowing and minimum efficacy estimated at roughly 8 years per treatment. The high dose pivotal trial GENEr8-1 pits val-rox against prophylaxis in a superiority study, with data expected in early 2021; however, BioMarin filed on an interim analysis from a subset of patients, with approval expected in August 2020.
SPK-8011 (Roche)	-	300	Hem A	once (curative)	Updates were minimal while Roche's acquisition of Spark was pending throughout 2019, but Roche recently noted plans to move to phase 3 in 2021; data at ASH 2018 showed strong factor expression in five patients at the key dose, but two patients saw immune responses that required on-demand factor VIII treatment. With minimal data and a timeline significantly behind competitors, we don't model significant sales here.
giroctocogene fitelparvovec SB-525 (Pfizer/Sangamo)	-	300	Hem A	once (curative)	SB-525 could be solid competition for BioMarin, but we don't have the duration data to tell, and it will likely arrive on the market two years behind BioMarin's Roctavian. As of June 2020, five patients in the high-dose cohort all had strong factor VII expression and no bleeds, with one patient 61 weeks into treatment at this dose (full 1-year data still to come). Pfizer started a lead-in study for phase 3 in October 2019, and expects to start a 63-pt phase 3 trial in H2 2020, with data 2022E.
SPK-8016 (Roche)	-	NM	Hem A/inhibitors	once (curative)	Roche expects to move this phase 1/2 AAV gene therapy for hem A inhibitor patients to phase 3 in 2021, although there has been little data released so far; there could be a data update potentially at ISTH in July 2020.
fidanacogene elaparvovec/ SPK-9001 (Spark, Pfizer)	-	NM	Hem B	once (curative)	A phase 2 study in 15 hemophilia B patients showed annualized reduction in bleeding rates by 98% with no severe adverse events. Levels of factor IX were improved with an enhanced manufacturing process. A phase 3 study started in summer 2019 and should complete in 2021.
EtranaDez/AMT-061 (uniQure/CSL)	-	NM	Hem B	once (curative)	Following solid mid-stage data, the phase 3 HOPE-B pivotal study of AAV5-based AMT-061 started observation in June 2018 and dosing in Feb 2019, achieving uniQure's target of 54 patients dosed as of March 2020. UniQure expects to have topline 26-week data by YE 2020 and to file in 2021, and partnered with CSL in June 2020.

Source: Morningstar, company reports.

Outlook for Key Hemophilia Products: Chronic Treatments

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Hemophilia subtype	Administration	Comments
Adynovate/Advate/ Recombinate (Takeda)	2,000	770	Hem A	Advate: every 2-3 days, Adynovate: 2x/wk	Strong Advate bleed rate data (42% of prophylaxis patients have zero bleeds) and pegylated Adynovate (excluded by UnitedHealth) should help Takeda defend against other replacement factors with similar convenience, but Roche's novel, differentiated Hemlibra launched broadly in 2019.
Kogenate/Kovaltry/Jivi (Bayer)	1,002	838	Hem A	3x/wk (Kogenate), 2-3x/wk (Kovaltry), every 5 days (Jivi)	Kogenate dominated the ex-US hemophilia market. Next-generation Kovaltry (which can allow twice-weekly dosing) and Jivi (approved 2018, can allow every 5 day dosing or even weekly dosing) are incremental improvements that will struggle to compete with differentiated offerings like Hemlibra.
Refacto/Xyntha (PFE)	425	284	Hem A	at least 2x/wk	Refacto is among the older generation of recombinant hemophilia A therapies, and concerns about higher rates of inhibitors (B-domain-deleted structure) have kept it from growing to the size of Advate and Kogenate.
Esperoct/NovoEight (NVO)	232	276	Hem A	every 4 days to weekly (N8-GP)	Novo launched its me-too Advate (NovoEight) at discounted prices to gain access to U.S. formularies, and its longer-acting product Esperoct was delayed to February 2020 due to manufacturing issues.
Eloctate/BIVV001 (Sanofi/Sobi)	1,251	1,031	Hem A	twice a week (Eloctate), once weekly (BIVV001)	While 30% of patients respond to every 5-day dosing, it lacks a significant convenience advantage over older factor replacement therapy and has a higher labeled bleed rate. Once-weekly BIVV001 entered phase 3 XTEND-1 in December 2019 and should have data in late 2021; we model a launch in 2023. However, once-weekly IV dosing still looks inconvenient relative to once-monthly subcu Hemlibra dosing.
Afstyla (CSL)	1,051*	1,160*	Hem A	twice a week	Approved in US in May 2016 and Europe in Jan 2017 as a twice-weekly product, Afstyla is a later entrant in a competitive market.
fitusiran/ALN-AT3 (Sanofi)	-	437	Hem A/ Hem B/ Inhibitors	once a month	Fitusiran's once-monthly, subcu dosing and mechanism of action (targeting antithrombin) could give it broad appeal across a variety of rare blood disorders; ATLAS data is expected H1 2021, with a potential 2022 launch. A hold due to a patient death in Sept 2017 led to a slight delay, but fitusiran resumed phase 3 at the end of 2017.
Hemlibra (RHHBY)	1,380	4,396	Hem A/ Inhibitors	once a week, bi-weekly, monthly	This bi-specific antibody has a novel structure that allows it to treat hemophilia A patients, regardless of whether they have inhibitors to factor VIII. With inhibitor patient approval in Nov 2017 in the U.S. and broader non-inhibitor approval in Oct 2018, we think Roche could rapidly replace bypassing agents for inhibitor patients in many markets and gradually replace factor VIII therapy for non-inhibitor patients.
NovoSeven (NVO)	1,234	934	Inhibitors	every 2 hrs (on-demand)	NovoSeven first lost share to Feiba prophylaxis and is now losing share to Roche's Hemlibra, although sales seem to be stabilizing as some patients still require on-demand treatment with NovoSeven. Sanofi's fitusiran (2022E launch) remains an additional threat.
Feiba (Takeda)	468	129	Inhibitors	every other day (prophylaxis)	Feiba's prophylaxis approval led to strong double-digit growth through 2015, as it gained share from NovoSeven, but sales have declined due to competition from (and safety interactions with) Hemlibra, and Sanofi's fitusiran remains a threat.
BeneFix (PFE)	488	344	Hem B	2-3x/wk	The former mainstay of hemophilia B therapy, BeneFix should continue to see erosion as new options gain traction.
Alprolix (Sanofi/Sobi)	621	712	Hem B	every 10-14 days	Longer-acting hemophilia B products like Alprolix appear to be differentiated from older generation Benefix, and Alprolix was first to market among long-acting products in the US (approved 2014 US and 2016 Europe).
Idelvion (CSL)	1,051*	1160*	Hem B	once weekly (up to every 14 days)	Idelvion's potentially every 2 week dosing could allow it to gain share from Alprolix. It was approved in Europe in May 2016 (same as Alprolix) and in the US in March 2016.
marstacimab/PF-06741086 (Pfizer)		NM	Hem A/ Hem B/ Inhibitors	once weekly sc	Pfizer's TFPI therapy entered phase 3 in early 2020 (data 2023E), but the recent failure of Novo Nordisk's TFPI therapy concizumab (phase 3 paused in March 2020 due to non-fatal thrombotic events) gives us pause.

Source: Morningstar, company reports. *CSL's total hemophilia sales

Noninsulin Diabetes Market

Outcomes data showing an improvement in cardiovascular events is shaking up the noninsulin market. Both the SGLT-2s (Jardiance and Invokana) and the GLP-1s (Victoza, Ozempic, and Trulicity) have shown cardio-protective characteristics that should drive increased penetration in the market at the expense of sulfonylureas, thiazolidinediones, and DPP-4s, which have largely been neutral to cardiovascular events. On the GLP-1 front, the data has been mixed with positive cardio-protective qualities coming from Novo Nordisk and Eli Lilly and a neutral profile from Sanofi's Lyxumia and Astra's Bydureon. The pricing weakness in the SGLT-2 class is concerning and surprising given the strong pricing in the GLP1 class.

Overview of Noninsulin Diabetes Drugs

					Dollar Branded Market Share	
Drug Class	**A1c lowering***	**Benefits**	**Disadvantages**	**U.S. Cost (Annual)**	**2019**	**2024E**
Sulfonylureas	-1.5	Long-term reduction in microvascular risk	Hypoglycemia, weight gain	$70	generic	generic
Metformin	-1.5	Effective	Rare lactic acidosis with impaired renal function	$70	generic	generic
Thiazolidinediones	-0.5 to -1.4	Increases insulin sensitivity	Cardiovascular risk, weight gain, edema	$140	generic	generic
GLP-1s	-0.7 to -1.6	Weight Loss	Injected, nausea, pancreatitis risk	$8,000	52%	64%
DPP-4s	-0.5 to -0.8	Weight Neutral	Slightly less effective, pancreatitis risk	$4,500	32%	13%
SGLT2s	-0.8 to -1.0	Weight Loss	Genital and urinary tract infections	$4,500	16%	23%

*Monotherapy

Source: Morningstar, company reports.

Overview of GLP-1s and SGLT-2s

GLP-1 Drugs	**Dosing**	**Key Point**	**Outcomes Study**	**2019 Sales ($B)**	**2024E Sales ($B)**
Byetta-AZN	Twice Daily	First to market, but low efficacy		0.7	0.4
Bydureon-AZN	Weekly	Inferior to Victoza	Mid-2017: no increased risks	-	-
Victoza-Novo	Once Daily	Favorable outcomes data	Early 2016: 13% reduction in cardio events	4.1	2.0
Ozempic-Novo	Weekly Inject/ Daily Oral	Better than Victoza and Trulicity	Mid-2016: 26% better on cardio events	1.7	6.0
Lyxumia-SNY	Once Daily	Late to market, inferio to Victoza	Mid-2015: no increased risks	0.0	0.0
Trulicity-LLY	Weekly	Non-inferior to Victoza	Mid-2018: 12% reduction in MACE-3	4.1	6.4

SGLT-2 Drugs	**Side Effects**	**Outcomes Study**	**2019 Sales ($B)**	**2024E Sales ($B)**
Invokana-JNJ	Ketoacidosis, acute kidney injury, and amputation	14% reduction in ~MACE	0.7	0.6
Forxiga-AZN	Ketoacidosis, acute kidney injury	7% reduction in MACE (not significant) 17% reduction in second primary endpoint of hospitalization for heart failure or CV death	1.5	2.4
Jardiance-LLY/BI	Fairly clean	14% reduction in ~MACE, 38% reduction in cardiovascular death	0.9	1.8
ertugliflozin-PFE/MRK	Clean so far	Only showed non-inferiority, creating a challenge for the drug	0.0	0.5

Source: Morningstar, company reports.

Insulin Market

We expect the global insulin market to stay flat around $19 billion between 2019 and 2024, as the emergence of biosimilar Lantus and Humalog and the resulting pricing pressure in the U.S. is countered by demand growth and uptake of Tresiba globally. We model annual volume growth in low-single digits, as the receptiveness of U.S. payers to biosimilar Lantus outweighs the anticipated price-stabilizing impact of next-generation insulins Tresiba and Toujeo. We expect Sanofi's global share of the insulin market to fall from 26% to 23% by 2024, as Lantus succumbs to further biosimilar competition and Toujeo fights for share against Tresiba (which gained labeling for hypoglycemia risk lowering in 2018). We think Novo Nordisk's share will grow from 48% to 52% over this same period, largely because of Tresiba. Eli Lilly should stay flat around 27%, as its biosimilar Lantus sees strong uptake but Humalog competition is emerging. While Sanofi has gained approval of Admelog, a biosimilar version of Eli Lilly's Humalog, the rapid-acting market is already heavily discounted because of years of payer pressure, which could leave less room for biosimilar penetration, and highlight the cost advantages that will continue to limit the number of players in the global insulin market.

Key Insulin Therapies

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Class of Insulin	Morningstar Takeaway
NovoRapid (NVO)	2,746	2,396	rapid-acting	The rapid-acting market has seen the longest stretch of competitive pricing among insulin therapies, given their relatively undifferentiated nature. Sanofi's biosimilar Humalog launched in 2018 and could further pressure the market, although initial biosimilar headway is in the lower-priced Medicaid segment.
Fiasp (NVO)	189	417	rapid-acting	Novo's ultra-rapid-acting insulin launched in late 2017, and the rapid action could be more appealing for patients requiring higher doses of insulin, including type 1 diabetics. However, we don't see the product as significantly differentiated from NovoRapid, limiting its potential.
Humalog/ Humalog Mix (LLY)	2,821	2,518	rapid/mix (soluble and crystalline Humalog)	The rapid-acting market has seen the longest stretch of competitive pricing among insulin therapies, given their relatively undifferentiated nature. Biosimilar Humalog launched in 2018, putting further pressure on price and market shares.
Admelog (SNY)	283	NM	short-acting (biosimilar Humalog)	Sanofi's biosimilar Humalog launched in 2018 in the U.S. and Europe, and while Novo and Lilly's PBM contracts could make it difficult for Sanofi to penetrate the rapid-acting market, we expect continued pricing pressure as a result. Sanofi is expected to first gain traction in the lower-priced Medicaid market segment.
NovoMix (NVO)	1,457	1,366	mix (soluble and crystalline NovoRapid)	NovoMix is still growing in emerging markets, but will likely be largely replaced by Ryzodeg. In many developed markets, combination of rapid-acting and long-acting insulins is preferred.
Ryzodeg (NVO)	150	260	mix (NovoRapid + Tresiba)	Ryzodeg's focus will be on developing markets, where insulin mix therapies are still widely used.
Lantus (SNY)	3,414	2,140	long-acting	Sales of this long-standing leader in the long-acting insulin market have been significantly eroded by the launch of Lilly's Basaglar (biosimilar version of Lantus), and Mylan's Semglee could add new biosimilar competition later in 2020.
Toujeo (SNY)	1,000	1,348	long-acting	Coverage of Toujeo fell with the launch of biosimilar Lantus, and the drug's growth trajectory has been hit by pricing pressure and competition from Novo's Tresiba.
Levemir (NVO)	1,415	785	long-acting	Even though Basaglar (biosimilar Lantus) is not a direct competitor, the launch weighed on Levenmir pricing, and Levemir is also losing share as Novo's Tresiba gains share.
Tresiba (NVO)	1,408	1,844	long-acting	Tresiba's strong profile has allowed it to gain share, although biosimilar Lantus (Lilly's Basaglar) has weighed significantly on U.S. pricing.
Basaglar (LLY)	1,113	1,497	long-acting (biosimilar Lantus)	Basaglar was launched in 2017 at tier 1 at UnitedHealth, the only plan to have an insulin on tier 1, and has gained strong share as it offers solid price discounts to branded counterparts.
Semglee (MYL)	-	NM	long-acting (biosimilar Lantus)	Launched in November 2018 in Europe, and likely to launch in the U.S. in late 2020 after June 2020 FDA approval. Prospects are mixed, as the exit of Merck's Lusduna signals less competition but perhaps a less attractive market opportunity, as prices have already been reduced to low levels.
Xultophy (NVO)	336	668	Tresiba + GLP-1 (Victoza)	FDA approved in November 2016, Xultophy launched in 2017, but uptake is still strongest for stand-alone Tresiba and Victoza, and a once-weekly version of insulin/GLP-1 combination is in the works.
Soliqua (SNY)	NM	302	Lantus + GLP-1 (Adlyxin)	FDA approved in November 2016, Soliqua launched in 2017, but uptake is still strongest for stand-alone basal insulin and GLP-1 therapies.
LAI287/icodec (NVO)	-	271	ultra-long-acting	Following positive phase 2 data for this once-weekly insulin, Novo plans to move into phase 3 by the end of 2020, and we assume approval in 2023. While this looks more convenient than current insulin options, efficacy benefit is so far unclear, as it was non-inferior to Lantus in phase 2. Potential to combine with once-weekly semaglutide (icosema) looks intriguing, and phase 1 of the combo has been completed.

Source: Morningstar, company reports.

Multiple Sclerosis Market

While the relapsing remitting market faces fewer dynamic changes, both the secondary progressive (30% of multiple sclerosis patients) and the primary progressive (10% of the multiple sclerosis patients) have new highly efficacious drugs emerging with Roche Ocrevus and Novartis' Mayzent, respectively. Generic Copaxone will likely reduce price increases in this market, where historical price increases average close 20% annually, but we expect largely stable branded prices going forward. A key swing factor for this market is whether the 2027 patent on Gilenya holds. The drug won an inter partes review that validated a dosing patent until December 2027, which may hold off generic competition for several more years, but we are still modeling in U.S. generic competition beginning in 2021.

Key Multiple Sclerosis Drugs

Product Indication & Mechanism of Action	Company	2024E Sales	Reduction in Relapse Rate	Reduction in Disability Progression	Frequency/Admin	Side Effects
Relapsing Remitting ~66% of diagnosed patients						
Betaseron (interferon beta-1b)	Bayer	0.4	0.31	0	every other day/subcu	flu-like symptoms, injection-site reactions, liver and blood count abnormalities
Avonex/Plegridy (interferon beta-1a)	Biogen	1.4	32%	18%	weekly/intramuscular (Plegridy biweekly)	flu-like symptoms, injection-site reactions, liver and blood count abnormalities
Rebif (interferon beta-1a)	Merck KGaA/Pfizer	0.7	0.32	0.3	3x per week/subcu	flu-like symptoms, injection-site reactions, liver and blood count abnormalities
Copaxone (immunomodulator)	Teva	0.8	29%	13%	daily or 3x a week/subcu	flu-like symptoms, injection-site reactions
Gilenya (S1P 1/3/4/5)	Novartis	0.8	54-60%	30-32%	daily/oral	temporary brachycardia, edema, liver injury,
Tecfidera (immune cell inhibitor)	Biogen	1.0	44-53%	34-38%	twice daily/oral	feeling flushed, lymphopenia, GI, headache, elevated liver and blood enzymes
Lemtrada (anti-CD52)	Sanofi	0.1	49% vs. INF	42% vs. INF	2 courses (5 days, 3 days, 12	malignancies, thyroid, autoimmune and kidney
Aubagio (slows T cells)	Sanofi	0.5	31%	32%	twice daily/oral	increased liver enzymes, birth defects, severe liver injury, neutropenia
Ocrevus (anti-CD20)	Roche/Biogen	7.1	46% vs. INF	40% vs. INF	6 months/IV	Infusion-site reactions, respiratory and skin infections
Zeposia/Ozanimod (S1P1/5)	Bristol	1.3	21-38% vs. INF	26-42% vs. INF	daily/oral	minimal; no evidence of increased cardiac or infection risk
Vumerity (NF E2)	Biogen	0.6	0.47	0.3	twice daily/oral	minimal; improved GI tolerability as compared to Tecfidera
Mayzent (S1P1/5)	Novartis	0.9	55%	21-33%	daily/oral	high blood pressure, raised liver enzymes, headache
Mavenclad (CdATP)	Merck KGaA	1.0	54-58%	0.47	oral/daily for two weeks a year	malignancies, fetal harm, respiratory infection, lymphopenia, herpes zoster
Ofatumumab (anti-CD20)	Novartis	1.3	51-59% vs. Aubagio	34% vs. Aubagio	monthly/subcu	injection-site necrosis, flu-like symptoms
Ponesimod (S1P1)	J&J	0.5	31% vs. Aubagio	Awaiting Data	daily/oral	temporary brachycardia ,flu-like symptoms, raised liver enzymes
Tysabri (alpha-4 integrin)	Biogen	2.0	55%-68%	24-42%	monthly/IV	serious brain infection (PML), infection, abdominal discomfort, fatigue
Secondary Progressive ~24% of diagnosed patients						
Gilenya (S1P 1/3/4/5)	Novartis					temporary brachycardia, edema, liver injury, potential increase in disability on stopping
Tysabri (alpha-4 integrin)	Biogen	2 total	55%-68%	24-42%	monthly/IV	serious brain infection (PML), infection, abdominal discomfort, fatigue
Mavenclad (CdATP)	Merck KGaA	1 total	54-58%	0.47	oral/daily for two weeks a year	malignancies, fetal harm, respiratory infection, lymphopenia, herpes zoster
Mayzent (S1P1/5)	Novartis	.9 total	55%	21-33%	daily/oral	high blood pressure, raised liver enzymes, headache
Ocrevus (anti-CD20)	Roche/Biogen	7.1 total	46% vs. INF	40% vs. INF	6 months/IV	Infusion-site reactions, respiratory and skin infections
Primary Progressive ~10% of diagnosed patients						
Ocrevus (anti-CD20)	Roche/Biogen	7.1 total	46% vs. INF	24% for PPMS	6 months/IV	Infusion-site reactions, respiratory and skin infections

Note: Efficacy data is versus placebo unless otherwise indicated. INF: interferon
Source: Morningstar, company reports.

Migraine Market

The migraine market is seeing significant innovation that should support strong growth, as many patients were poorly served by triptan drugs (Imitrex) and Botox, and most patients have tried treatment and discontinued. With a list price around $7,000 for novel CGRP antibodies (but significant discounts of at least 30% beyond this), we think the global market for the drugs in our coverage universe (excluding Biohaven) could be worth more than $5 billion by 2024, with almost 10 million patients in the developed markets as candidates for treatment. The top drugs from Amgen/Novartis, Eli Lilly, Teva, and Lundbeck eliminate migraines in 10%-20% of patients and cut attacks in half in more than 50% of patients, making this a competitive marketplace, and we saw heavy promotion, including one year of free drug. Differentiation is largely on method of administration (pen, autoinjector, or syringe) and frequency of injections (ranging from monthly to quarterly). First-generation oral CGRP receptor antagonists from Boehringer Ingelheim, Bristol, and Merck failed as acute treatment for migraine because of liver toxicity and formulation difficulties, but a new generation of oral CGRPs, led by AbbVie's Ubrelvy and Biohaven's Nurtec, are on the market in acute indications, and Nurtec and AbbVie's atogepant are poised to compete in the prophylaxis market. Eli Lilly's Reyvow, another oral with a differentiated mechanism, should also compete well in the acute market, complementing prophylaxis with the firm's injectable Emgality.

Key Migraine Drugs: Injectables

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Type	Dosing	Population	Headache days per month	Comment
Botox (AbbVie/Allergan)	600	600	onabotulinum-toxinA	multiple small injections, every 12 weeks	chronic migraine prophylaxis	7.8-9.2 day reduction v 6.4-6.9 days placebo	Previously the only approved treatment for chronic migraine, Botox can cost around $5,000 and contributes 20% of Botox's roughly $3 billion in annual revenue (less than 200,000 migraine patients treated).
Aimovig/ erenumab (Amgen/Novartis)*	409	1,445	CGRP-receptor antibody	sc (autoinjector or prefilled syringe), 1x/mo	episodic and chronic migraine (prophylaxis)	ARISE (episodic, 3 mo): 2.9 day reduction v 1.8 placebo. STRIVE (episodic, 6 mo): 3.2-3.7 day reduction v 1.8 placebo. Chronic prevention, phase 2b(3 mo): 6.6 day reduction v 4.2 placebo. LIBERTY (episodic, failed multiple tx): >50% reduction,migraine days v placebo.	Amgen's May 2018 U.S. approval put it in a first-to-market position ahead of Lilly and Teva, although CVS preferred Emgality and Ajovy with 2019 formularies (Aimovig is included in 2020, likely with price concessions). Monthly, single, small-volume, auto-injection could be most convenient option for patients. Targeting the receptor could be more effective at a lower dose.
Emgality/ galcanezumab (Lilly)	163	1,211	CGRP antibody	sc (pen or prefilled syringe), 1x/mo	episodic and chronic migraine (prophylaxis), episodic cluster headache	Evolve-1 (episodic) 4.6-4.7 days vs 2.8 days placebo. Evolve-2 (episodic): 4.2-4.3 days vs 2.3 days placebo. REGAIN (chronic): 4.6-4.8 days vs 2.7 days placebo.	Approved in the US in Sept 2018 in episodic and chronic migraine, Lilly's drug looks similar to Aimovig, but with Lilly's popular pen technology. Lilly also received approval in cluster headache prevention (positive phase 3 in episodic cluster headache) in June 2019. Teva filed a lawsuit to halt its launch based on patent infringement, but Lilly challenged several Teva patents via IPR in Aug 2018 (PTAB concluded Teva's patents were valid in March 2020), so patent battles are still in progress.
Ajovy/ fremanezumab (Teva)	96	700	alpha/beta CGRP antibody	sc (pre-filled syringe--autoinjector approved Jan 2020), 1x/mo or quarterly	episodic and chronic migraine (prophylaxis)	HALO CM (chronic): 4.3-4.6 day reduction, monthly/quarterly, v 2.5 days placebo. HALO EM (episodic): 3.7/3.4 day reduction, monthly/quarterly v 2.2 days placebo.	Approved in Sept 2018, Teva's Ajovy has a quarterly dosing option, and efficacy looks similar to other CGRPs. However, failure in both chronic and episodic cluster headaches trials could make it difficult to compete with Lilly. It will face a crowded market and was excluded from Express Scripts' national formulary and by UnitedHealth in 2019.
Vyepti/ eptinezumab (Lundbeck)	0	294	CGRP antibody	quarterly IV (30 min)	episodic and chronic migraine (prophylaxis), acute migraine	PROMISE 1 (episodic) 3.9-4.3 day reduction on 100mg-300mg v 3.2 days placebo at wk 12. PROMISE 2 (chronic) 7.7-8.2 day reduction on 100mg-300mg v 5.6 days placebo at week 12.	Lundbeck's $2 billion acquisition of Alder in 2019 gave them rights to eptinezumab, approved in Feb 2020 for migraine prevention as Vyepti, but efficacy to date does not look differentiated from earlier entrants, and the IV administration convenience is debatable. Pricing could be less competitive in the medical benefit channel. Lundbeck expects data in acute migraine by year-end 2020.

Source: Morningstar, company reports.

*Aimovig sales figures represent global sales (combining Amgen's U.S./Japan and Novartis' ROW sales).

Key Migraine Drugs: Oral/Intranasal Treatments

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Type	Dosing	Population	Headache days per month	Comment
Ubrelvy/ ubrogepant (AbbVie/Allergan)		300	oral CGRP	1-2x per attack	acute migraine treatment	ACHIEVE 1: 19-21% pain free at 50-100mg doses v 12% placebo (5 liver enzyme elevations, all explained) ACHIEVE 2: 50mg similar to ACHIEVE 1, 25 mg insignif v placebo (4 liver enzyme elevations, one was placebo, unrelated)	Approved in December 2019, Ubrelvy is the first oral CGRP to market and the first CGRP approved for acute use. Liver toxicity ended development of earlier oral CGRPs, but ubrogepant passed two liver safety studies in healthy volunteers in October 2018, and the drug was approved with no black box warning. We expect AbbVie's migraine entrenchment with Botox could help uptake, and ICER's price benchmark of $4,200-$4,600 is quite close to the $4,900 list price.
Nurtec ODT/ rimegepant (Biohaven)		NM	oral CGRP	1x per attack	acute migraine treatment and migraine prevention	Acute migraine data: 19.2-19.6% pain free (2 studies) v 14.2-12% placebo Prevention data: 10.7 migraines per month during observation, followed a 4.5 reduction for Nurtec and 3.7 reduction for placebo.	Approved in Feb 2020 in the acute indication based on three phase 3 trials and with positive phase 3 data in prevention in March 2020, Nurtec could become both the first oral prevention therapy and first approved for both indications. Biohaven has seen no liver imbalance in phase 3 trials to date. Longer half life and faster onset could be advantages over Ubrelvy. Pricing is within ICER's price benchmark of $4,200-$4,600.
atogepant/ AGN-241689 (AbbVie/Allergan)		313	oral CGRP	1-2x daily	episodic and chronic migraine (prophylaxis)	Phase 2b: 3.55-4.23 day reduction v 2.85 days placebo (12 weeks)	With positive phase 2b/3 data in June 2018, atogepant is now in phase 3 studies in episodic prevention (data 2H 2020E) and chronic prevention (data 2021E). We think AbbVie has 70% probability of approval with filing in 2022.
vazegepant / BHV-3500 (Biohaven)		NM	intranasal CGRP	1x per attack	acute migraine treatment	Pain free at two hours: 23.1% 20 mg, 22.5% 10 mg, and 15.5% placebo.	Phase 2/3 data was positive in December 2019, showing rapid onset of action and efficacy through 48 hours, with no evidence of hepatotoxicity. A non-oral treatment could be particularly useful for patients with nausea and vomiting. Biohaven needs one more efficacy study before filing for approval.
Reyvow/ lasmiditan (Lilly)		535	oral 5-HT1F	1-2x per attack	acute migraine treatment	SPARTAN: 29-39% migraine free at two hours v 21% placebo.	Lilly received approval in October 2019 and launched in Feb 2020 at $640 for 8 pills, and the drug could be used alongside Lilly's preventative CGRP therapy Emgality. We expect Reyvow to compete with AbbVie/Allergan's oral CGRP Ubrelvy, which should also launch in 2020. Dizziness and sleepiness side effects could somewhat limit uptake (and appeared to limit ICER's cost effectiveness review).

Source: Morningstar, company reports.

Alzheimer's Market

Despite the 2016 failure of Eli Lilly's amyloid antibody solanezumab, there are several disease-modifying Alzheimer's disease drugs still in development, typically with improved clinical trial design, including pre-screening for amyloid with imaging, and targeting patients at the earliest stages of the disease. Aducanumab dominates our sales forecast for this therapeutic area. While the drug failed a futility analysis in March 2019, it was resurrected in October 2019 following data from additional patients, and we now assign aducanumab a 40% probability of approval in 2021.

Key Alzheimer's Drugs

Drug (Firm)	Mechanism	2024E Sales ($ Mil)	Phase (Data Timing)	Population	Analysis
aducanumab (BIIB)	beta-amyloid	2500	Filing 2H 2020	Prodromal to mild AD	Aducanumab's development path has been a rollercoaster, but we currently model a 40% probability of approval and $3 billion in probability-weighted sales by 2029, with approval possible in 2021 (Biogen filed in July 2020).
gantenerumab (RHHBY)	beta-amyloid	350	Phase 3 (2021E interim)	Prodromal to mild AD	While Roche's other amyloid antibody crenezumab failed at interim analysis in phase 3 in 2019, gantenerumab continues in phase 3 and could have an interim analysis in 2021. Gantenerumab's current phase 3 trials test a higher dose than used in its previous failed Scarlet Road study. We think the drug looks similar to aducanumab, but a 24-month trial and high-dose availability to APOE4 carriers throughout the trial could make it easier for gantenerumab to meet endpoints, and subcu dosing would be an advantage. A brain shuttle version of gantenerumab, which should more easily penetrate the brain, is in phase 1.
BAN2401 (BIIB/Eisai)	beta-amyloid	NM	Phase 3 (2022E)	Prodromal to mild AD	Biogen and Eisai generated mixed data in phase 2 in 2018, with positive overall signals of efficacy, but a confusing subgroup analysis. The partners have pushed forward into phase 3 development, with data expected in 2022, although differentiation from aducanumab is unclear.
gosuranemab/ BIIB092 (BIIB)	tau	NM	Phase 2 (2021E)	MCI, Mild Alzheimer's	Gosuranemab failed in progressive supranuclear palsy but is still in development in Alzheimer's disease trial Tango. Gosuranemab's tau mechanism of action could someday prove complementary to amyloid (aducanumab) therapies. Biogen also has other tau programs (BIIB076 and BIIB080) in earlier development, but none of these are included in our valuation.
zagotenemab/ LY3303560 (LLY)	tau	NM	Phase 2 (2021E)	Early symptomatic Alzheimer's	In a phase 2 efficacy study, but facing multiple tau competitors and uncertainty around the mechanism of action.
donanemab LY3002813 (LLY)	N3PG	NM	Phase 2 (2021E)	Early symptomatic Alzheimer's	Phase 2 efficacy study Trailblazer-Alz is continuing, and the drug would have a differentiated mechanism of action of approved, although data so far is scarce.
DNL747/788 (Denali, Sanofi)	RIPK1	NM	DNL 788 entering development	Early symptomatic Alzheimer's	DNL747 was specifically designed to cross the blood brain barrier and target the TNF pathway, which is involved in inflammation, immunity, and cell death. While phase 1 data in June 2020 showed off-target, molecule-specific side effects for DNL747, Denali and Sanofi are moving forward with backup compound DNL788.

Source: Morningstar, company reports.

Immuno-Oncology Market

We expect striking efficacy and strong pricing power to drive immuno-oncology sales, with strong sales in lung cancer and support from several other cancer types. We expect wide usage of immuno-oncology drugs due to their strong efficacy across patient types, despite stronger responses in certain patient groups (such as high PD-L1 positivity). Combinations are the next wave of development, with leadership in CTLA4, LAG3, and others likely to drive the first major combinations. Additionally, we view the adjuvant setting as the next major market opportunity for expansion with the immunology drugs, with approvals already gained in adjuvant melanoma.

Approvals in Immuno-Oncology

	Bristol's Opdivo		Merck's Keytruda		Roche's	AstraZeneca's
Cancer Indication	**U.S.**	**Europe**	**U.S.**	**Europe**	**Tecentriq**	**Imfinzi**
1st Line NSCLC	2020E	2020E	Oct. 2016 (PDL1+50%)** Aug. 2018 (non-Sq + Alimta) Oct. 2018 (Sq)	Jan. 2017 (PDL1+50%), Sept. 2018 (Non-Sq. + Alimita), March 2019 (Sq. + chemo)	Dec. 2018 U.S., Mar. 2019 EU	2020-21E
2nd Line NSCLC/Other	2015^	Apr. 2016	Oct. 2015 (PDL1+)	Aug. 2016 (PDL1+)	Oct. 2016 U.S., Sept. 2017 EU	2018
Melanoma	Dec. 2014	Jun. 2015	Sept. 2014	Jul. 2015	2020E	NA
Melanoma Adjuvant	Dec. 2017	Jul. 2018	Feb. 2019	Dec. 2018	NA	NA
Renal	Nov. 2015	Apr. 2016	Apr. 2019 (Inlyta)	Sept. 2019	2020E	NA
Bladder	Feb. 2017*	Jun. 2017	May 2017	Sept. 2017	May 2016 U.S.* Sept. 2017 EU	May 2017* U.S.
SCLC	Aug. 2018	NA	Jun. 2019	2020E	Mar. 2019 U.S. (first line) Sept. 2019 EU (first line)	2020E
Liver	Sept. 2017	2020E	Nov. 2018 (2nd line)	2019	May-20	NA
Head and Neck	Nov. 2016	Apr. 2017	Aug. 2016*	Sept. 2018	NA	2020E
Colon/Rectal	Aug. 2017***	NA	May 2017***	2020E	2020E	NA
Hodgkin's	May 2016*	Nov. 2016	Mar. 2017	May 2017	NA	NA
Esophageal	June 2020	2021E	Sept. 2017	2019	NA	NA
Gastric	NA	NA	Sept. 2019	NA	NA	NA
Triple Neg. Breast	NA	NA	2020E	2020E	Mar 2019 U.S., Aug. 2019 EU	NA
Cervical	NA	NA	June 2018	NA	NA	NA

*Accelerated approval. **Expanded to all PDL1 expression levels in May 2017. ***MSI high (microsatellite instability). ^March 2015 Sq. October 2015 Non-Sq, Note: Multiple myeloma trials are on hold.
Source: Morningstar, company reports.

PD1/PDL1 Outlook for 2024

		Market Share By Firm									
Cancer Indication	PD-1/PDL1 Market Size ($ B)	Bristol-Myers	Roche	Merck	Astra	Pfizer/ Merck KGaA	Sanofi/ Regeneron	U.S. Annual Death Rate (000s)	Mutation Rate	Percentage Positive for PDL1	Market Outlook
NSCLC Nonsquamous	16	10%	25%	60%	2%	0%	3%	134	High	35-95%	Merck's first-mover advantage and excellent data will help secure share, but combination with TIGIT and CTLA4 drugs could help Roche and Bristol.
NSCLC Squamous	6	10%	5%	80%	2%	0%	3%				
NSCLC Stage 3	3	0%	0%	5%	95%	0%	0%	NA	High	NA	Astra's Pacific data gives it a lengthy lead here.
NSCLC Adjuvant/Neo	5	15%	35%	35%	15%	0%	0%	NA	High	NA	Merck and Roche lead in adjuvant while Bristol and Astra lead in neoadjuvant
Melanoma/Adjuvant	4	55%	10%	35%	0%	0%	0%	10	Very High	40-100%	Merck's fast follower in adjuvant and Roche's MEK/BRAF combinations look competitive.
Renal	3	58%	0%	35%	0%	7%	0%	15	Low	15-24%	Merck has strong data here, but Bristol's first-mover advantage and strong data in intermediate/poor (75% of patients) supports leadership as well.
Bladder	2	10%	10%	25%	5%	50%	0%	16	High	28-100%	Good OS data from Pfizer/Merck KGaA provides strong competitive positioning.
SCLC	3	5%	55%	5%	35%	0%	0%	24	High	NA	Strong data from Roche and Astra should displace Bristol's first-mover advantage.
Liver	3	20%	60%	20%	0%	0%	0%	27	NA	NA	Roche's strong data with Avastin should let it surpass first movers Bristol and Merck.
Head and Neck	2	15%	0%	75%	10%	0%	0%	13	Moderate	NA	Merck has first-mover advantage with first-line approval.
Blood*	1	44%	0%	44%	10%	2%	0%	>35	Moderate	Ranges	Merck and Bristol share leadership with an initial focus on Hodgkin's lymphoma.
Esophageal*	2	30%	0%	70%	0%	0%	0%	16	High	42%	Merck and Bristol hold leadership here, although Merck looks ahead in approval timelines.
Other*	4	25%	30%	30%	0%	5%	10%		Ranges		breast (Merck, Roche, Pfizer/Merck KGAA), basal cell carcinoma (Sanofi), cutaneous squamous cell carcinoma (Sanofi), and ovarian (Roche) are key
Total Sales ($ B)	**53**	**9.9**	**11.3**	**24.4**	**5.5**	**1.4**	**1.1**				
2024 Market Share		**18%**	**21%**	**46%**	**10%**	**3%**	**2%**				
Consensus ($ B)	**44**	**9.6**	**6.4**	**21.5**	**4.1**	**1.0**	**1.3**				
Consensus Market Share		**22%**	**15%**	**49%**	**9%**	**2%**	**3%**				

*Limited clinical data lowers our market estimate. ^Initially focused on Microsatellite instability-high (MSI-H), which is about 15% of colorectal cancer and 4%-5% of metastatic colorectal cancer.
Source: Morningstar, company reports.

Non-HER2-Positive Breast Cancer

With Roche having built an $8 billion business around HER2-positive breast cancer (20% of the market), the CDK4/6 drugs target a different 65% of the breast cancer market (ER+/HER2-). Pfizer controls a solid first-mover advantage with Ibrance ($120,000 per year, close to double Herceptin's price), but competition from Novartis and Eli Lilly is catching up. While Novartis' drug doesn't look much different from Ibrance, Eli Lilly's drug showed better monotherapy data and the ability to target brain cancer (1-16% of breast cancer patients). Also, Pfizer's Ibrance has yet to show a survival benefit in the first-line setting while both drugs from Eli Lilly and Novartis have shown this benefit. The failure of Ibrance in the adjuvant setting is disappointing, but Lilly's Verzenio did show a benefit in the high-risk adjuvant setting and Novartis' drug still has a chance in this important market.

Overview of Key CDK4/6 Drugs: 2024E Sales Ibrance: $7.2 Billion; Verzenio: $4.5 Billion; and Kisqali: $1.6 Billion

Study	Tumor	Combination	PFS months (drug vs. placebo)	Hazard Ratio	Grade 3/4 Side Effects	Data Point
Pfizer's Ibrance (approved 2015)						
PALOMA-1* (1st Line Breast)	ER+, HER-	Letrozole	20.2 vs. 10.2	0.59	Neutropenia: 54%	OS of 37.5 months versus 34.5 was not statistically significant (HR: 0.897)
PALOMA-2 (1st Line Breast)	ER+, HER-	Letrozole	24.8 vs. 14.5	0.58	Neutropenia: 66% Diarrhea: 1%	OS data expected in 2021-2022
PALOMA-3 (2nd Line Breast)	ER+, HER-	Fulvestrant	9.5 vs. 4.6	0.46	Neutropenia: 66% Diarrhea: 0%	Interim stop, Sicker group with 36% prior chemo users, OS was not stat. sig., but was 19% better
PALOMA-4 (1st Line Breast)	ER+, HER-	Letrozole	PFS data in Aug. 2020			Asian Population
PEARL (Breast, post aromatase)	ER+, HER-, Resistant to Aromatase Inh.	Exemestane or Fulvestrant	No benift versus capecitabine in Dec. 2019			Largely showed Ibrance needs to be taken earlier.
PATINA (1st Line Breast)	HER+	Herceptin/Perjeta + Endocrine therapy	PFS data in May 2021			
PENELOPE-B (High Risk) Adjuvant	HER normal	Endocrine therapy	Disease Free Survival Data in late 2020			
PALLAS (Stage II/III) Adjuvant	ER+, HER-	Endocrine therapy	Stopped early due to failure to work.			
Lilly's Verzenio (approved 2017)						
MONARCH 1 (2nd Line Breast)	ER+, HER-	None	6.0 single arm study	NA	Neutropenia: 27% Diarrhea: 20%	Very sick group with 100% prior chemo users
MONARCH 2 (2nd Line Breast)	ER+, HER-	Fulvastrant	16.4 vs. 9.3	0.55	Neutropenia: 27% Diarrhea: 13%	OS HR of 0.757
MONARCH 3 (1st Line Breast)	ER+, HER-	Anastrozole or Letrozole	NR vs. 14.7	0.54	Neutropenia: 21% Diarrhea: 10%	
monarcHER* (3rd Line Breast)	**HER+**	Herceptin plus Fulvestrant	8.3 vs. 5.7	0.67		Phase II
MONARCH plus (Breast)	ER+, HER-	Several	NR vs. 14.7	0.50		
JUNIPER (2nd Line **Lung**)	KRAS mut.	None	PFS data in June 2018			Did not show a OS benefit
neoMONARCH* (Early Breast)-Adj.	ER+, HER-	Anastrozole/loperamide	Change in Ki67 in Aug. 2016: >91% had drop in Ki67 level vs. 63% placebo (p<0.001)			
monarchE (Adjuvant Breast)	ER+, HER-	Endocrine Therapy	Positive top line data in June 2020			
Novartis' Kisqali (approved 2017)						
MONALEESA-2 (1st Line Breast)	ER+, HER-	Letrozole	25.3 vs. 16	0.57	Neutropenia: 60% Diarrhea: 1%	Interim stop
MONALEESA-3 (1st and 2nd Line Breast)	ER+, HER-	Fulvestrant	33.6 vs. 19.2	0.546		OS HR: 0.724
MONALEESA-7 (Premenopausal-Breast)	ER+, HER-	Tamoxifen, Goserelin, or Aromatase	23.8 vs. 13.0	0.57		19% of breast cancer is diagnoses under the age of 50, OS HR: 0.71
NATALEE	ER+, HER-	Endocrine therapy	Data expected in 2022			
EarLEE-1 (Adj. Breast-High Risk)	ER+, HER-	Endocrine therapy	Disease Free Survival Data in mid-2020			
EarLEE-2 (Adj. Breast-Medium Risk)	ER+, HER-	Endocrine therapy	Disease Free Survival Data in 2025			

*Phase 2 study. Note: Key aromatase inhibitors include anastrozole, letrozole, and exemestane.

Source: Morningstar, company reports.

Non-Hodgkin's Lymphoma Market

We expect the global non-Hodgkin's lymphoma market to grow from $7.6 billion in 2019 to $14.1 billion in 2024 (13% CAGR). In follicular lymphoma, Roche launched Gazyva in the first-line setting in 2018, and the Rituxan/Revlimid combination was approved in the relapsed setting in 2019 based on strong Augment data. In aggressive lymphomas, Polivy (launched 2019), and CD19 therapies represent growth opportunities. CD19 therapies take the form of curative CAR-T therapy (Gilead/Novartis launches in 2018, liso-cel launch 2020E, off-the-shelf ALLO-501 in trials) as well as off-the-shelf antibodies (Incyte/MorphoSys tafasitamab to launch in late 2020). In the long term, we expect bispecific antibodies to compete in both settings, led by Roche's mosunetuzumab and Sanofi/Regeneron's REGN1979.

Overview of Key NHL Drugs

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Mechanism	Approved Indications (in Testing)	NHL Analysis
Revlimid (Bristol)	840	705	IMiD	MCL, RR FL	Studies like Remarc (DLBCL), Relevance (1L FL), and Robust (non-GCB DLBCL) all failed to improve on prior regimens, but strong Augment data in RR FL led to FDA approval in 2019.
Rituxan (Roche)	4145	1722	CD20	DLBCL, FL	Rituxan is a standard backbone of care in NHL, but biosimilar threats are entering the market.
Gazyva (Roche)	375	1,368	CD20	FL	Gazyva failed to beat Rituxan in Phase 3 GOYA (DLBCL), but beat Rituxan in Phase 3 GALLIUM (FL induction and maintenance), and we expect strong uptake for first-line patients with indolent lymphomas.
Imbruvica (AbbVie/J&J)	1564	2718	BTK	MCL (FL)	Imbruvica failed in a phase 3 study in 1L DLBCL in 2018, and data from the Phase 2 DAWN study in RR FL was disappointing, so we're bearish on the outcome of Phase 3 SELENE in RR FL (data 2020E). However, Imbruvica is already well-established in mantle-cell lymphoma.
Calquence (AstraZeneca)	41	735	BTK	MCL (FL)	Recently approved in mantle cell lymphoma, Calquence is in small mid-stage studies with Rituxan in FL, but given Imbruvica's weak data in FL, we're less optimistic about sales potential in this indication.
Kymriah (Novartis)	56	583	CD19 (CAR-T)	RR DLBCL	First approved in ALL, Kymriah arrived second-to-market among CD19-targeting CAR-T cell therapies in DLBCL (behind Gilead's Yescarta) in May 2018, and DLBCL-specific manufacturing issues have held back sales in this indication.
Yescarta (Gilead)	449	1,115	CD19 (CAR-T)	RR DLBCL	Yescarta launched late 2017 as a treatment for patients who have failed at least two prior lines of therapy in DLBCL, based on impressive efficacy and durable complete response rates, despite the risk of serious side effects. Yescarta data in 2L DLBCL (ZUMA-7, 2020E) and future approval in new indications (ALL, FL) could further expand sales, but competition from other CAR-T therapies (Bristol's liso-cel), off-the-shelf CAR-T therapy (Allogene's ALLO-501) and off-the-shelf antibody therapy (Polivy and tafasitamab) will weigh on growth.
Liso-cel/JCAR017 (Bristol)	0	1058	CD19 (CAR-T)	(RR DLBCL)	Liso-cel could launch by late 2020 to compete with Yescarta and Kymriah in DLBCL, and safety data so far has looked differentiated and could allow for outpatient use.
Polivy (Roche)	51	1,140	CD79b ADC	RR DLBCL, (1L DLBCL)	Roche launched Polivy in 2019 based on strong phase 2 data, and this looks like a solid option for older patients ineligible for transplants or CAR-T therapy. Phase 3 study Polarix in first-line DLBCL is in progress, with data expected 2020-21.
mosunetuzumab and glofitamab (Roche)	0	390	CD20/CD3 bispecific	(FL, DLBCL)	Mosunetuzumab (from Genentech) and glofitamab (from Roche) both generated solid early-stage data, and are in testing in both DLBCL and FL. Mosunetuzumab looks likely to have a stronger safety profile, and glofitamab looks more effective but with a slightly worse safety profile--both could compete with Regeneron's REGN1979, which appears to have better efficacy but more side effects.
REGN1979 (Regeneron)	-	540	CD20/CD3 bispecific	(FL, DLBCL)	REGN 1979 had impressive data at ASH 2019 (77% CR in FL at doses at least 5mg, CR 42% in DLBCL at doses at least 80mg) , but it's difficult to determine efficacy relative to Roche's program as both firms escalate dosing, and safety (grade 3-4 CRS in 6% of patients) was concerning. Regeneron is in a multi-arm pivotal phase 2 study, with filing expected in 2021-22. Regeneron is also planning chemo combination studies.
epcoritamab/GEN3013 (AbbVie/Genmab)		40	CD20/CD3 bispecific	(FL, DLBCL)	Epcoritamab is in dose expansion in phase 1/2 testing, with data and potential initiation of pivotal programs in 2020; initial dose escalation data at ASCO 2020 showed solid safety and potential promising efficacy, even if patient numbers remain small. A collaboration with AbbVie was announced in June 2020.
tafasitamab/MOR208 (Incyte, Morphosys)		320	CD19 antibody	(DLBCL)	L-MIND data (in combination with Revlimid in 2L or 3L DLBCL) position tafasitamab for approval in August 2020. We expect use in patients too frail for CAR-T, similar to Polivy, and duration of response and PFS look competitive with Polivy (tafasitamab also offers a chemo-free regimen). The drug is also in a phase 1b trial in first-line DLBCL comparing tafasitamab combinations to R-CHOP, the longstanding standard of care. Dat against another Rituxan-based standard, BR, in RR DLBCL should be available in 2022 (B-MIND).
ALLO-501 (Allogene)		NM	CD19 CAR-T (DLBCL, FL)		Initial data from the Alpha study at ASCO 2020 showed the potential of this off-the-shelf CAR-T therapy in DLBCL and FL. After lymphodepletion with ALLO-647, 19 patients who received ALLO-501 (after a median of 4 prior therapies) had strong responses, with half of patients on the high dose of ALLO-647 achieving a complete response (4/8). With no neurotoxicity, only 1 case of grade 3 CRS, and the ability to redose to achieve a CR, ALLO-501 looks promising.

Note: NHL: non-Hodgkin's lymphoma; FL: follicular lymphoma (a subset of NHL); DLBCL: diffuse large B-cell lymphoma (a subset of NHL); MCL: mantle cell lymphoma.
Source: Morningstar, company reports.

Chronic Lymphocytic Leukemia Market

We expect the global chronic lymphocytic leukemia market to grow from $5.9 billion in 2019 to $10.9 billion in 2024 (13% CAGR). Gazyva's strong data helps preserve Roche's CLL franchise, but AbbVie/J&J's Imbruvica and Roche/AbbVie's Venclexta are poised to significantly expand this market over the next five years. We think first-line expansion of Imbruvica (with Gazyva or Rituxan) and Venclexta (with Gazyva) could expand curative options.

Overview of Key Chronic Lymphocytic Leukemia Drugs

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Mechanism	Approved Indications (in Testing)	CLL Analysis
Rituxan (Roche)	700	273	CD20	1L, 2L CLL	Rituxan has long been the standard of care in CLL, but is losing share to newer treatments, and biosimilar headwinds lower our long-term forecast.
Gazyva (Roche)	177	432	CD20	1L CLL	Roche's next-generation CD20 is approved in 1L CLL with chlorambucil. We expect that recent positive 1L CLL data with Imbruvica (iLLUMINATE) and Venclexta (CLL14) to expand usage.
Imbruvica (AbbVie/J&J)	4,122	5,645	BTK	1L del17p, 1L, 2L CLL	Imbruvica has been the clear standard of care in RR CLL for years and has a strong presence in 1L CLL, although Venclexta-based combinations with Roche's CD20 antibodies are increasingly prescribed. Positive phase 3 data in 1L CLL with Gazyva (iLLUMINATE) and with Rituxan (E1912) should drive additional uptake in the first-line setting.
Calquence (AstraZeneca)	123	1,364	BTK	1L CLL, 2L CLL	Approved in mantle cell lymphoma in 2017, Calquence's biggest opportunity is in CLL, where it received FDA approval in November 2019. Head-to-head data versus Imbruvica in the refractory setting is due in 2021.
Venclexta (AbbVie/Roche)	713	2,034	Bcl-2	17p 2L CLL, 2L CLL with Rituxan, AML, 1L CLL with Gazyva	Initially marketed in the 17p deletion niche of CLL, Venclexta approval has expanded thanks to positive results in the Phase 3 MURANO study in the broader RR CLL population in combination with Rituxan and with Gazyva in the first-line setting. AbbVie is testing a fixed duration Venclexta/Imbruvica combination in CLL, with data expected in 2021.
Iiso-cel (Bristol)	-	187	CD19	(RR CLL)	Poised for FDA approval in late 2020 in DLBCL, liso-cel has shown a strong 46% complete response rate after several lines of prior therapy in CLL (early-stage data at ASH 2019).

Source: Morningstar, company reports.

Multiple Myeloma Market

We expect the global multiple myeloma market to grow from $18 billion in 2019 to $23 billion in 2024 (5% CAGR), as generic competition to Bristol's Revlimid weighs on otherwise strong growth from products like J&J/Genmab's Darzalex and Bristol's Pomalyst and new launches. BCMA-targeted therapies are making their way toward the market, with Glaxo's antibody drug conjugate potentially reaching the market first, followed by higher-efficacy CAR-T therapies from Bristol and J&J in 2020 and 2021. Weekly bispecific antibodies targeting BCMA from J&J, Regeneron, Bristol, and Amgen are starting to produce early data in dose-finding studies, and relative to CAR-T, we think they could represent a slightly less effective but cheaper and more convenient option for patients by 2023.

Overview of Key Multiple Myeloma Drugs: Non-BCMA

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Mechanism	MM Analysis
Darzalex (J&J/Genmab)	2997	7,325	CD38	First approved as monotherapy in 4L+ MM, Darzalex rapidly expanded into 2L MM with Pollux (combo with Revlimid) and Castor (combo with Velcade) studies, and the drug was approved in NDMM in 2018 and 2019 (Alcyone study with Velcade and Maia with Revlimid in transplant ineligible, Cassiopeia in transplant-eligible), cementing its position in first-line treatment. Subcu dosing approved in 2020 further expands convenience.
Sarclisa (Sanofi)	-	300	CD38	Sarclisa was approved in March 2020 in third-line or later multiple myeloma following strong data in combination with Pomalyst, and Kyprolis combination data in RRMM from the Ikema study was also positive in June 2020, comparing favorably with a similar Candor study for Darzalex. However, Darzalex's first-mover advantage, solid efficacy and safety profile, and entrenched position create a high bar for direct CD38 competition, unless first-line data (expected in 2022) is differentiated.
Revlimid (Bristol)	10,500*	5,876	IMiD	Revlimid is likely to remain the backbone of combination therapy with novel agents, and usage in the front-line setting in combination with Velcade is expanding. Usage as a maintenance treatment in transplant patients is expanding, and sales globally are benefiting from longer PFS with combos (Velcade, Kyprolis, and Darzalex).
Pomalyst (Bristol)	2,500*	3,527	IMiD	Pomalyst is a leading option in 3L MM, and a 2L MM combination study with Velcade (MM-007 OPTIMISMM) had strong data at ASCO 2018. However, 2L MM is competitive with Darzalex + Revlimid/Velcade as a key regimen.
Velcade (Takeda, J&J)	1748	392	Proteasome Inhibitor	Velcade's patent expiration will put significant pressure on Takeda's (U.S.) and J&J's (international) sales, although launch of subcutaneous generics has delayed the hit in the U.S. until at least 2021. Approval with Darzalex in 1L MM boosts potential, but Darzalex data with Revlimid in this setting is stronger.
Kyprolis (Amgen)	1,044	1,346	Proteasome Inhibitor	Strong Aspire and Endeavor data boost Kyprolis use in RRMM, and Arrow (once-weekly) data showed strong efficacy (approved Oct 2018). We think Kyprolis will continue to grow to $1.5 billion, as duration of therapy for patients increases, and as more convenient once-weekly administration is rolled out.
Ninlaro (Takeda)	712	1,305	Proteasome Inhibitor	Approved in RRMM (with Revlimid), Ninlaro has a niche among elderly patients who would prefer an oral proteasome inhibitor (over Velcade or Kyprolis). Ninlaro had solid data at ASH 2018 in the maintenance setting (post-transplant), but expansion into first-line transplant-ineligible multiple myeloma looks uncertain, following the failure of Tourmaline-MM2 (adding to Revlimid) but success of Tourmaline-MM4 (first-line maintenance add-on vs placebo) in 2020.

Note: MM: multiple myeloma; RRMM: relapsed and refractory MM; NDMM: newly diagnosed MM.
*Estimated 2019 sales (full-year sales undisclosed because of Bristol's acquisition of Celgene).
Source: Morningstar, company reports.

Overview of Key Multiple Myeloma Drugs: Pipeline, BCMA-Targeting Therapies

Drug (Firm)	2019 Sales ($ Mil)	2024E Sales ($ Mil)	Mechanism	MM Analysis
belantamab mafodotin (Glaxo)	-	370	BCMA ADC	Efficacy so far does not look competitive with CAR-T cell therapies targeting BCMA, but belantamab is poised for approval in 2020, perhaps the earliest BCMA approval, and this could initially be an appealing option as an off-the-shelf therapy.
ide-cel/bb2121, bb21217 (Bristol, Bluebird)	-	700	BCMA CAR-T	Ide-cel could receive approval based on the Karmma study in late 2020, despite regulatory delays, with potential to be first-to-market among BCMA therapies. Updated Karmma data at ASCO 2020 showed an 81% response rate and 35% complete response rate among 54 patients at the highest dose, which is strong but doesn't compare well to J&J's evolving data. Bristol aims to move usage earlier with ongoing studies, but bispecific antibodies (J&J, Amgen, Regeneron) and other CAR-T therapies (J&J) could threaten uptake. Initial data for bb21217 was encouraging at ASH 2019, but the drug is still in phase 1.
orva-cel/JCARH125 (Bristol)		NM	BCMA CAR-T	Acquired with Celgene/Juno, this CAR-T program has had promising early data (most recent, a 92% response rate and 22/62 patients achieving at complete response in the Evolve study, as of ASCO 2020) and serves as a backup to Bluebird-derived CAR-T programs.
JNJ-4528 (J&J/Legend)	-	1,100	BCMA CAR-T	J&J's CARTITUDE-1 study reported first data at ASH 2019, but responses deepened in an update at ASCO 2020, with a 100% response rate in 29 patients continuing and a stringent response rate growing from 69% to 86% (nearly undetectable disease), which should position it as the leading efficacy BCMA therapy. The pivotal portion of CARTITUDE-1 is fully enrolled and should have data by year-end 2020, according to Legend filings, and a larger Cartitude-2 study is in progress.
Teclistamab/JNJ-7957 (J&J)		500	BCMA bispecific	In a phase 1 study at ASCO 2020, the drug showed a 67% response rate at the highest dose so far (8 of 12 patients), in a group of relapsed multiple myeloma patients with a median of 6 prior treatments. Higher doses are being tested and the response also appears to improve with time. Weekly dosing looks like an option, putting this potentially on par with Regeneron's bispecific program.
AMG 420/AMG 701 (Amgen)	-	500	BCMA bispecific	Early data for AMG 420 showed solid efficacy, but continuous infusion and potential side effects of this administration limited its viability. We await phase 1 data from once-weekly drug AMG 701 in 2020, which could be an option for sicker patients ineligible for transplant.
REGN 5458/5459 (Regeneron)		500	BCMA bispecific	REGN5458 has an encouraging safety profile so far with no neurotoxicity, and no grade 3 or higher cytokine release syndrome, with impressive efficacy at the first two weekly doses (ORR 75%, CR 75%), but only among 4 patients. Regeneron is testing higher doses and early testing of REGN 5459, which has different CD3 binding affinity. We expect a phase 2 update later in 2020.
CC-93269 (Bristol)		NM	BCMA bispecific	Data at ASH 2019 showed the potential for a once-monthly bispecific. Early phase 1 data show strong efficacy (highest dose so far has 89% ORR and 44% CR among 9 patients, median 5 prior tx with 77% refractory to Darzalex), and a strong safety profile (3% grade 3 or higher CRS and 30% grade 3 or higher infections).
talquetamab/ JNJ-7564 (J&J)		270	GPRC5D/CD3 bispecific	J&J is studying this novel targeted multiple myeloma bispecific in early-stage development as monotherapy and in combination with Darzalex, although little data is available.
iberdomide, CC-92480 (Bristol)	-	NM	IMiD	CC-92480 had encouraging efficacy data in refractory patients (6 prior lines) at ASCO 2020 with phase 1/2 ongoing, and iberdomide is entering the phase 2 Icon study in 3L+ patients in 2020. The goal is to find a product that could have broader activity than Revlimid, perhaps without dexamethasone (more frail patients).
Venclexta (AbbVie/Roche)	-	232	Bcl-2	Phase 3 Bellini data (with Velcade) in 2019 in multiple myeloma showed a strong progression-free survival benefit, but higher proportion of deaths limits potential; the Canova trial (with dexamethasone) continues in the 20% of patients with t(11;14) positive disease and should have data in 2021.

Note: MM: multiple myeloma, RRMM: relapsed and refractory MM, NDMM: newly diagnosed MM.
Source: Morningstar, company reports.

HIV Drug Market

Overall, we expect the HIV market to grow from $26.6 billion in 2019 to a peak of $27.4 billion in 2020, and then decline slightly with generic Truvada/Atripla entry in the U.S. to roughly $26.6 billion by 2024. We expect declines to remain in single-digit territory for the next several years as patent losses in the U.S. come in waves, in 2025 for Odefsey and Descovy, 2029 for Genvoya, and 2033 for Biktarvy. We expect the market to remain largely split between Gilead (60% share) and Glaxo (30% share). While Gilead lost some market share to Glaxo (Tivicay's high barrier to resistance among integrase inhibitors boosted uptake of Tivicay and combo pill Triumeq), Gilead's new TAF-based regimens (which have better bone and renal safety profiles than the old TDF regimens) and the non-boosted integrase regimen Biktarvy help Gilead maintain share of the global market. Glaxo recently brought two-drug regimens Juluca (Edurant/Tivicay: 2018) and Dovato (Tivicay/lamivudine: 2019) to market to simplify treatment and reduce side effects, although we expect long-term efficacy data will be needed to secure stronger uptake given Biktarvy's excellent safety profile. Glaxo has several programs in late-stage development, including an oral attachment inhibitor (to address roughly 5% of patients who are heavily pretreated) and a long-acting integrase cabotegravir (as prophylaxis).

Overview of Key HIV Drugs (Gilead)

Drug (Firm)	2024E Sales ($Mil)	Class	Approval Year	Efficacy (HIV-1 RNA < 50 copies/mL)	Analysis
Genvoya (GILD)	1,676	2 NRTIs + integrase + booster	2015	87% at week 96 in naïve pts vs 85% Stribild.	Launched in 2016, Genvoya offers renal and bone density benefits over older generation HIV combo pills. Growth slowed in 2018 as Gilead's next-gen combo Biktarvy launched and turned negative in 2019, although additional to China's reimbursed drug list in 2020 could help stabilize sales.
Descovy (GILD)	2,633	2 NRTIs	2016	Genvoya: 92% at week 48 in naïve pts and 96% at week 48 in switch patients. Discover trial (PrEP v Truvada): 96 wk data showed non-inferiority with incidence rate of 0.16/100 person years v 0.30 for Truvada	With renal and bone density benefits over Truvada, Descovy is already seeing strong uptake, and approval was extended to prophylaxis in October 2019. While two-year data from the Discover trial point to similar efficacy for Descovy and Truvada, Descovy's TAF backbone supported significant bone and renal safety advantages over Truvada (TDF backbone), as in HIV treatment trials.
Odefsey (GILD)	962	2 NRTIs + NNRTI	2016	Treatment naïve 77% at week 96 (83% <100,000 copies at baseline and 71% in those >100,000 at baseline) and switch 89% at week 48	With renal and bone density benefits over Complera, Odefsey is launching strongly.
Biktarvy (GILD)	9,096	2 NRTIs + integrase	2018	Treatment naïve: non-inferior to Triumeq in study 1489 (92.4% v 93%, 82% v 84% at week 144) and to Tivicay + Descovy in study 1490 (89.4% v 92.9% at wk 48 and 82% v 84% at wk 144) Switches: non-inferior to boosted PI regimens at wk 48 in study 1878 (92.1% v 88.9%)	Gilead's latest combination regimen is having a strong launch, with similar efficacy to Glaxo's regimens and arguably better safety. In study 1489, there was slightly less nausea in the bictegravir arm (10% v 23%), and Triumeq patients had more frequent GI, neuropsychiatric, and sleep symptoms. In study 1490, Biktarvy had fewer treatment related adverse events (20% v 28%).
lenacapavir/ GS-6207 (GILD)	80	capsid inhibitor	2021E	Phase 1b data in March 2020: single subcu dose led to significant HIV RNA reductions by day 10 versus placebo. July 2020: therapeutic concentrations sustained for at least six months after single 900 mg dose.	This novel Gilead drug could prevent resistance by targeting the capsid shell around HIV RNA, and dosing could be as infrequent as every six months (subcu injection). The drug entered larger phase 2/3 studies in late 2019 in both treatment experienced and treatment-naive patients in combination with oral drugs (data 2021E, to file in in treatment experienced setting in 2021). Gilead expects to begin a phase 1 trial in once-weekly PrEP in H2 2020, and the drug could also be combined with recently licensed neutralizing antibodies or with a long-acting version of bictegravir (just entering clinical studies).

Source: Morningstar, company reports.

Overview of Key HIV Drugs (non-Gilead)

Drug (Firm)	2024E Sales ($Mil)	Class	Approval Year	Efficacy (HIV-1 RNA < 50 copies/mL)	Analysis
Triumeq (GSK)	2,671	2 NRTIs + integrase	2014	SINGLE: 71% v 63% Atripla at 144 wks, tx naïve	Glaxo's integrase-based combo has seen strong uptake, but risk of heart attack with abacavir is still debated. Gilead's NRTI backbone (TAF) is generally perceived as the safest, while Glaxo's integrase appears the most effective.
Tivicay (GSK)	2,050	integrase	2013	SPRING-2: 82% v 78% with Isentress-based regimen	Glaxo's strong integrase continues to perform well in the face of competition from Gilead.
Juluca (GSK)	1,164	NNRTI + NRTI	2018	SWORD maintenance (Edurant + Tivicay): 95% at week 48 (non-inferior to current regimens), 89% at week 100	Offers a simpler, potentially lower-side effect option for HIV patients for maintenance following triplet therapy, but uptake has been slow, likely due to patient/physician migration away from NNRTI-containing regimens, the risk of resistance in a two-drug regimen, and the need to initiate patients on another therapy prior to Juluca.
Dovato (GSK)	1,635	Integrase (Tivicay) + NRTI (lamivudine)	2019	GEMINI 1 and 2: 48-week pooled data for Dovato v Truvada + Tivicay: 91% v 93% 96-week pooled data: 86% v 89.5% TANGO: can maintain viral suppression at 48 weeks after switch from three-drug TAF regimens to Dovato	Although Dovato's April 2019 approval offers a simpler, potentially lower-side effect option for new and switching HIV patients, we think doctors remain focused on established long-term efficacy of three-drug regimens, despite the $27,000 price tag for Dovato (26% less than Biktarvy's list price). Gemini data show that this regimen is capable of producing strong efficacy without risking treatment resistance, supported by two-year data, although non-inferiority to the Truvada-based regimen at 96-weeks showed a trend to better efficacy than Dovato, particularly in patients with CD4+ levels less than 200 (87% v 68%).
Cabenuva (GSK)	750	cabotegravir/rilpivirine (CARLA regimen)	2020E	ATLAS: 1-yr data showed non-inferior efficacy for CARLA (92.5%) to oral combos (95.5%) in patients stable on oral for 6 mo or more. FLAIR: after two years, similar efficacy for CARLA (86.6%) to Triumeq (89.4%) in patients switched from Triumeq after 20 wks of therapy. ATLAS-2M: 2M non-inferior to 1M (0.8% more patients with 50 copies or more), virologic failure rate higher for 2M (1.5% v 0.2%), but 5 cases of pre-existing resistance in 2M arm.	This once-monthly injectable combo could create a new long-acting class of HIV therapy, but a complete response letter in December 2019 tied to process controls delayed FDA approval beyond the first quarter of 2020. Painful intramuscular injections could limit uptake, but bi-monthly injections, which appear to have similar efficacy as once-monthly injections (data Mar 2020), could improve potential. A large pre-exposure prophylaxis (PrEP) study of bi-monthly dosing was stopped early due to strong efficacy versus Truvada (66% more effective), although the powering was recently changed to non-inferiority instead of superiority, and the difference appeared to be due to adherence.
Rukobia (fostemsavir) (GSK)	174	attachment inhibitor	2020	BRIGHTE study in heavily treated pts: 60% achieved HIV-1 RNA <40 copies/mL as of week 96	Viiv filed for approval of fostemsavir in Dec 2019, and following a July 2020 approval, we expect it could be added to combination therapies in very sick HIV patients unable to suppress virus levels on other therapies.
Delstrigo/ Pifeltro (MRK)	162	Delstrigo: 2NRTIs (TDF/3TC) + NNRTI (Pifeltro: NNRTI)	2018	Treatment naïve v Atripla: 48-wk 84% v 81%, 96-wk 78% v 74%. Treatment naïve v Prezista regimen: 48 wk 84% v 80%	Delstrigo (TDF, lamivudine, and doravirine) proved similar in efficacy to Sustiva-containing regimens, but with superior lipid profiles and fewer neuropsychiatric side effects. However, integrase-based combination regimens are preferred, which may limit sales of Delstrigo and stand-alone doravirine (Pifeltro).
Prezista/ Symtuza (JNJ)	1,637*	Prezista: PI Symtuza: 2 NRTIs + PI + booster	Prezista: 2006 Symtuza: 2018	Amber: tx naïve: 91% v 88% TDF-based control, 48 wks Emerald: virologically-suppressed: 95% v 94% TDF-based control at 48 wks	J&J's combination of Gilead's TAF with its own Prezista allows for a one-pill Prezista regimen, but still requires a booster. We expect integrase-based regimens to continue to take priority in new patients, but this could be a safer, more convenient regimen for patients previously taking TDF with Prezista.
Edurant (JNJ)	937	Edurant: NNRTI Complera: 2NRTIs + NNRTI Odefsey: 2NRTIs + NNRTI Juluca: integrase + NNRTI	Edurant/ Complera: 2011 Odefsey: 2016 Juluca: 2018	SWORD maintenance (Edurant + Tivicay): 95% at week 48 (non-inferior to current regimens), 89% at week 100 Odefsey: treatment naïve 77% at week 96 (83% <100,000 copies at baseline and 71% in those >100,000 at baseline) and switch 89% at wk 48	Edurant use is still significant in newer combinations, as part of Odefsey and Juluca combination regimens. However, combination use favors integrase-based regimens.
islatravir/ MK-8591 (MRK)	389	NRTTI (nucleoside reverse transcriptase translocation inhibitor)	2023E		Early data in 2019 in 12 patients indicated than a plastic rod implant of this novel drug could protect patients from infection for one year. Merck started a phase 2 for a once-monthly oral PrEP regimen in Sept 2019. Merck has also experimented with using the drug as part of a two-drug treatment regimen (with doravirine), but a Phase 2b comparison vs the relatively weak comparator Delstrigo showed similar efficacy and higher virologic failure rates (5.6% v 3.2%). We expect the drug could be tested in different combinations, but creating a once-weekly treatment regimen could be challenging. Phase 3 data should report out in 2021-2023.

Source: Morningstar, company reports. *combines J&J's Prezista-related sales with Gilead's Symtuza sales share

Hepatitis C Market

The hepatitis C market peaked in 2015 at almost $24 billion globally. Treatment rates peaked in early 2015 in the U.S. and in late 2015/early 2016 in Japan. Pricing has also fallen, due to tougher negotiations with payers to expand access, more patients qualifying for 8-week regimens, and a higher percentage of U.S. patients being treated via more heavily discounted public payers (like the VA). In 2018, AbbVie's launch of the 8-week, $26,000 regimen Mavyret was in full swing, and we estimate this has pushed net prices in HCV to $15,000 per cure (a contrast to initial list prices of $84,000 per cure for Gilead's Sovaldi). We expect the HCV market to become more stable following severe price pressure in 2018, and we assume that the market declines from $6.4 billion in 2019 to $3.4 billion in 2024. Global market share, dominated by Gilead through 2017, has since been split fairly evenly between Gilead and AbbVie, and we expect AbbVie to slightly gain share going forward, given Mavyret's slightly more convenient profile. Use in China could also be a factor, and although Epclusa gained reimbursement in 2020, Mavyret should soon follow (approved in May 2019 and could compete by 2022).

Overview of Key Hepatitis C Drugs

Drug (Firm)	Sales 2024E ($ Mil)	Class	Key Genotypes	Efficacy	Advantages
Gilead (Epclusa, Harvoni, Vosevi)	1,322	Epclusa: nuc + pan-genotypic NS5A	1-6	Epclusa data: GT1-6 (98% cure rate despite 21% cirrhosis and 28% tx-exp) 12 wk GT1,2,4,5,6: 99% 12 wk GT3 95%	Epclusa will not replace Harvoni in developed markets, as this 12-week regimen isn't competitive for GT1 patients (45% of patients are eligible for 8-week Harvoni, and a real-world Cigna study revealed a 98% cure rate with Harvoni). However, strong GT3 data for the 12-week regimen, and consistently strong efficacy across genotypes, mean that it has replaced Sovaldi outside of GT1 and serves as a strong option for developing markets, as its pan-genotypic nature eliminates the need for genotyping prior to treatment (Epclusa was added to the national reimbursed list in China in 2020, ahead of Mavyret). Vosevi's profile makes it a good salvage option for patients (12-week regimen approved in the US, 8 week in Europe).
AbbVie (Mavyret)	1,844	PI + NS5A	1-6	tx-naive or IFN/SOF exp, non-cirrhotic: 8-wk GT 1 99%, 8-wk GT2 98% tx-naive or IFN/SOF exp, compensated cirrhosis: 12-wk GT1 99%, GT2 100% tx-naive GT3: 8-wk 94.9% non-cirrhotic, 12-wk 98% cirrhotic 12-wk PI-exp 92% 16-wk NS5A exp: 94%	AbbVie's next-generation regimen, Mavyret does not require ribavirin and covers all key genotypes, and was approved as an 8-week regimen in non-cirrohotics in 2017. This becomes a more convenient option than Gilead's Epclusa for non-GT1 patients. The regimen looks similar to Gilead's offerings in convenience in genotype 1, where Harvoni is often used for only 8 weeks, although a wider range of patients could be eligible for Mavyret 8-week dosing.

Source: Morningstar, company reports.

Appendix: Portfolio Summaries

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
AbbVie (ABBV)					
	Humira	expiring patents	Immunology	$ 6,200	$ 9,800
	Restasis	expiring patents	Dry Eye	$ 40	$ 100
	Botox Therapeutic	expiring patents	Several	-	-
	Linzess	inline	Irritable bowel syndrome	$ 927	$ 947
	Imbruvica	inline	Hematology	$ 7,096	$ 7,775
	Venclexta/venetoclax	inline	hematology	$ 2,906	$ 3,051
	Mavyret	inline	hepatitis C	$ 1,844	$ 1,506
	Orilissa/Elagolix	inline	endometriosis/uterine fibroids	$ 722	$ 911
	Risankizumab	inline	Immunology	$ 3,197	$ 3,681
	Rinvoq	inline	immunology/RA (rheumatoid arthritis)	$ 2,992	$ 2,957
	Botox Cosmetic	inline	Wrinkle remover	$ 4,206	$ 4,816
	Juvederm	inline	Facial filler	$ 1,114	$ 810
	Ubrelvy	inline	Acute migraine	$ 300	$ -
	Vraylar	inline	CNS, bipolar depression, schizophrenia	$ 1,527	$ 1,544
	Veliparib (ABT-888)	pipeline	Cancer	$ 276	$ 138
	Atogepant	pipeline	Migraine	$ 313	$ 276
	ABBV-3373	pipeline	Rheumatoid arthritis	-	-
Amgen (AMGN)					
	Epogen	expiring patents	nephrology (anemia)	$ 400	$ 350
	Neulasta	expiring patents	oncology (neutropenia)	$ 1,300	$ 1,200
	Aranesp	expiring patents	nephrology/oncology (anemia)	$ 1,000	$ 1,200
	Repatha (evolocumab)	inline	cholesterol	$ 2,500	$ 1,800
	Enbrel	inline	-	$ 1,700	$ 3,600
	Otezla (apremilast)	inline	psoriasis/psoriatic arthritis	$ 3,000	$ 3,200
	Prolia	inline	osteoporosis	$ 3,200	$ 3,400
	Evenity/Romosozumab (AMG 785)	inline	osteoporosis	$ 800	$ 850
	Xgeva	inline	prevention of bone mets	$ 2,800	$ 2,400
	Kyprolis	inline	oncology (multiple myeloma)	$ 1,300	$ 1,400
	Blincyto (blinatumomab)	inline	hematological oncology	$ 350	$ 450
	Imlygic (Talimogene	inline	oncology (melanoma)	$ 250	$ 200
	Amjevita (biosimilar Humira)	inline	immunology	$ 750	$ 1,100
	Parsabiv / etelcalcetide	inline	nephrology (SHPT)	$ 1,000	$ 1,100
	Kanjinti (biosimilar Herceptin)	inline	breast cancer	$ 675	$ -
	Aimovig / erenumab / AMG 334	inline	migraine prophylaxis	$ 725	$ 900
	Avsola/biosimilar Remicade (ABP 710)	inline	immunology	$ 225	$ 275
	Mvasi (biosimilar Avastin)	inline	oncology	$ 660	$ 360
	biosimilar Rituxan (ABP 798)	pipeline	RA/lymphoma	$ 300	$ 150
	Sotorasib/AMG 510	pipeline	Oncology (NSCLC, CRC)	$ 400	$ 600
	tezepelumab	pipeline	severe asthma	$ 400	$ 500
	omecamtiv mecarbil (AMG 423)	pipeline	heart failure	$ 300	$ -
	AMG 420 / AMG 701	pipeline	multiple myeloma	$ 500	$ 100

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
AstraZeneca (AZN)					
	Crestor	expiring patents	cardiovascular	$ 649	$ 875
	Nexium	expiring patents	Acid reflux/stomach ulcer	$ 7,079	$ 1,077
	Symbicort	expiring patents	COPD	$ 1,602	$ 1,718
	Pulmicort	expiring patents	COPD	$ 1,110	$ 1,591
	Brilinta	expiring patents	cardiovascular	$ 1,493	$ 1,949
	Farxiga	inline	diabetes	$ 2,630	$ 3,032
	Tagrisso	inline	oncology	$ 7,702	$ 7,119
	Onglyza	inline	diabetes	$ 333	$ 307
	Lynparza	inline	oncology	$ 3,254	$ 3,561
	Bevespi	inline	COPD	$ 444	$ 372
	Calquence/acalabrutinib	inline	CLL, MCL	$ 2,099	$ 2,154
	Imfinzi/durvalumab	inline	oncology	$ 5,534	$ 4,050
	Fasenra/Benralizumab	inline	Asthma/COPD	$ 1,827	$ 2,166
	Lokelma/ZS-9	inline	Hyperkalemia (high potassium)	$ 1,002	$ 523
	Enhertu/DS-8201	inline	cancer	$ 900	$ 583
	Koselugo/Selumetinib	inline	cancer	$ 120	$ 215
	Roxadustat	pipeline	anemia/CKD	$ 586	$ 863
	Tremelimumab	pipeline	oncology	$ 450	$ 235
	Anifrolumab	pipeline	lupus	$ 280	$ 235
	PT010/Triple LAMA/LABA/ICS	pipeline	respiratory	$ 330	-
	Capivasertib	pipeline	cancer	-	-
	Nirsevimab/MEDI8897	pipeline	RSV prevention	-	-
	Brazikumab	pipeline	immunology	$ 150	-
	tezepelumab	pipeline	severe asthma	$ 450	$ 370
Bayer (BAYRY)					
	Xarelto	inline	deep vein thrombosis	€ 3,944	€ 3,234
	Kogenate/Kovaltry/Jivi	inline	hemophilia	€ 740	€ 821
	Eylea	inline	ophthalmology	€ 2,053	€ 2,512
	Aliqopa/Copanlisib	inline	oncology	€ 367	€ 404
	Vitrakvi/larotrectinib	inline	oncology	€ 300	€ 317
	darolutamide/ODM-201	inline	oncology	€ 553	€ 679
	finerenone	pipeline	oncology	€ 328	€ 307
	vericiguat	pipeline	oncology	€ 188	€ 73
	molidustat	pipeline	Kidney Disease	€ 0	€ 0
	vilaprisan	pipeline	Uterine fibroids	-	€ 69

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Biogen (BIIB)					
	Tecfidera	expiring patents	MS	$ 1,000	$ 3,300
	Spinraza	inline	spinal muscular atrophy	$ 1,400	$ 1,700
	Tysabri	inline	MS	$ 1,900	$ 1,600
	Avonex/Plegridy	inline	MS	$ 1,400	$ 1,000
	Rituxan/Gazyva (U.S.)	inline	oncology, arthritis	$ 800	$ 850
	Ocrevus (ocrelizumab)	inline	MS	$ 1,300	$ 1,000
	Benepali (Enbrel biosimilar)	inline	immunology	$ 550	$ 600
	Flixabi (Remicade biosimilar)	inline	immunology	$ 150	$ 150
	Imraldi (Humira biosimilar)	inline	immunology	$ 350	$ 500
	Vumerity (diroximel fumarate)	inline	MS	$ 550	$ 500
	aducanumab (BIIB037)	pipeline	Alzheimer's	$ 1,800	$ 2,500
	Cirara / BIIB093 (glibenclamide)	pipeline	large hemispheric infarction	$ 200	$ 150
	opinicumab (BIIB033)	pipeline	MS	$ 350	$ 100
	Timrepigene emparvovec / BIIB111	pipeline	choroideremia	$ 250	$ 150
	BIIB092	pipeline	Alzheimer's	$ -	$ -
	BIIB067 (IONIS-SOD1)	pipeline	ALS	$ 150	$ 150
	BIIB059	pipeline	Lupus (CLE, SLE)	$ 200	$ -
	BIIB054	pipeline	Parkinson's disease	$ 300	$ -
	BIIB112/NSR-RPGR	pipeline	X-linked retinitis pigmentosa	$ 100	$ 60
	BAN2401	pipeline	Alzheimer's	$ -	$ 50
BioMarin (BMRN)					
	Kuvan (sapropterin)	expiring patents	mild/moderate PKU	$ 200	$ 150
	Aldurazyme (laronidase)	inline	MPS I	$ 100	$ 100
	Naglazyme (galsulfase)	inline	MPS VI	$ 425	$ 450
	Vimizim (GALNS)	inline	Morquio A Syndrome, MPS IVA	$ 800	$ 750
	Brineura / cerliponase alfa (BMN-190)	inline	CLN2 disease (Batten disease)	$ 250	$ 250
	Palynziq / pegvaliase (PEG-PAL)	inline	PKU (classic)	$ 450	$ 650
	vosoritide (BMN-111)	pipeline	Achondroplasia	$ 1,100	$ 550
	Val-rox (BMN-270)	pipeline	hemophilia A	$ 1,100	$ 750
Bristol (BMY)					
	Sprycel	expiring patents	CML	$ 609	$ 756
	Revlimid (lenalidomide)	expiring patents	hematological oncology	$ 5,876	$ 7,917
	Orencia	expiring patents	RA	$ 1,962	$ 2,707
	Abraxane (protein-bound paclitaxel)	expiring patents	oncology (breast/lung/pancreatic)	$ 253	$ 591
	Eliquis	inline	cardiovascular	$ 12,636	$ 12,375
	Yervoy	inline	oncology	$ 1,856	$ 2,041
	Opdivo	inline	oncology	$ 9,891	$ 9,563
	Pomalyst (pomalidomide)	inline	hematological oncology	$ 3,527	$ 3,347
	Inrebic/fedratinib	inline	myelofibrosis	$ 596	$ 361
	Reblozyl/luspatercept (ACE-536)	inline	beta thalassemia, MDS	$ 885	$ 1,077
	Relatlimab	pipeline	oncology	$ 375	$ 170
	BMS-986165	pipeline	immunology	$ 473	$ 53
	NKTR-214	pipeline	oncology	$ -	$ -
	BMS-986177	pipeline	cardiovascular	$ -	$ -
	Zeposia/ozanimod	pipeline	MS, ulcerative colitis, Crohn's disease	$ 1,634	$ 1,471
	Liso-cel/JCAR017	pipeline	DLBCL, CLL	$ 1,245	$ 835
	CC-486 (oral aza)	pipeline	blood cancer	$ 1,051	$ 620
	bb2121/bb21217	pipeline	Relapsed multiple myeloma	$ 700	$ 883
	BGB-A317	pipeline	solid tumors	$ 250	$ -

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Gilead (GILD)					
	Truvada	expiring patents	HIV	$ -	$ 100
	Atripla	expiring patents	HIV	$ 25	$ 50
	Harvoni (Sovaldi + GS-5885/ledipasvir)	inline	hepatitis C	$ 150	$ 1,600
	Genvoya (TAF-based "Stribild")	inline	HIV	$ 1,700	$ 2,400
	Epclusa(sofosbuvir+velpatasvir/GS-5816)	inline	hepatitis C	$ 1,200	$ 1,200
	Odefsey (TAF-based "Complera")	inline	HIV	$ 1,000	$ 1,300
	Descovy (TAF-based "Truvada")	inline	HIV	$ 2,600	$ 2,800
	Complera/Eviplera	inline	HIV	$ 75	$ 75
	Stribild	inline	HIV	$ -	$ 100
	Vemlidy (TAF)	inline	HBV	$ 1,500	$ 600
	Vosevi (sofosbuvir+velpatasvir + voxilaprevir)	inline	hepatitis C	$ 50	$ 1,600
	Yescarta (axi-cel)	inline	hematological oncology	$ 1,200	$ 1,200
	Biktarvy (B/F/TAF)	inline	HIV	$ 9,100	$ 10,000
	Veklury/remdesivir	inline	SARS-CoV-2 (COVID-19)	$2,500 (2021)	$1,400 (2022)
	filgotinib	pipeline	immunology	$ 1,600	$ 1,000
	Lenacapavir/GS-6207	pipeline	HIV	$ 100	$ -
	Ziritaxestat/GLPG-1690	pipeline	IPF	$ 300	$ 400
	GLPG-1972	pipeline	osteoarthritis	$ 200	$ 150
	magrolimab	pipeline	MDS, AML, lymphoma, solid tumors	$ 300	$ 300
	GLPG-1205	pipeline	IPF	$ 100	$ -
	GS-9674	pipeline	NASH, PBC/PSC	$ 100	$ -
	GS-0976	pipeline	NASH	$ 100	$ -
GlaxoSmithKline (GSK)					
	Seretide/Advair	expiring patents	Asthma/COPD	£849	£889
	Breo/Relvar	inline	Asthma/COPD	£1,165	£994
	Anoro	inline	COPD	£783	£705
	Trelegy	inline	COPD	£1,890	£1,738
	Shingrix	inline	Zoster Vaccine (shingles)	£3,254	£3,342
	Juluca (dolutegravir + Edurant)	inline	HIV (maintenance)	£962	£758
	Tivicay	inline	HIV	£1,694	£1,388
	Triumeq	inline	HIV	£2,207	£1,868
	Nucala	inline	asthma	£1,107	£1,171
	Zejula	inline	cancer	£866	£916
	Dolutegravir + lamivudine	inline	HIV	£1,351	£952
	fostemsavir/ BMS-663068	pipeline	HIV	£144	£218
	Cabotegravir	pipeline	HIV	£625	£620
	GSK2857916	pipeline	hematological oncology	£299	£754
	Dostarlimab	pipeline	cancer	£103	£334
	Gepotidacin	pipeline	antibiotic	-	£76
	M7824	pipeline	cancer	-	£543
	Otilimab GM-CSF	pipeline	Rheumatoid Arthritis	£150	£116
	GSK33596609	pipeline	cancer	£25	£136
	Daprodustat	pipeline	Chronic kidney disease	£220	£223

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Johnson & Johnson (JNJ)					
	Remicade	expiring patents	immunology	$ 1,605	$ 1,675
	Prezista	expiring patents	antiretroviral (HIV)	$ 682	$ 1,785
	Zytiga	expiring patents	prostate cancer	$ 1,069	$ 647
	Invega Sustenna/Trinza	expiring patents	schizophrenia	$ 3,146	$ 4,710
	Stelara	expiring patents	psoriasis, Crohn's	$ 9,774	$ 9,448
	Simponi	inline	RA	$ 2,355	$ 2,456
	Imbruvica	inline	hematology	$ 5,065	$ 6,374
	Xarelto	inline	deep vein thrombosis	$ 3,458	$ 2,503
	Invokana	inline	diabetes	$ 617	$ 441
	Darzalex	inline	multiple myeloma	$ 7,433	$ 7,325
	Tremfya/guselkumab	inline	Psoriasis	$ 2,853	$ 2,963
	Opsumit	inline	pulmonary arterial hypertension	$ 1,923	$ 1,930
	Uptravi	inline	pulmonary arterial hypertension	$ 1,405	$ 1,577
	Erleada/ARN-509	inline	prostate cancer	$ 2,734	$ 1,831
	esketamine	inline	depression	$ 623	$ 1,110
	Erdafitinib/JNJ-493	inline	cancer	$ 391	$ 463
	Pimodivir	pipeline	Influenza	$ 216	$ -
	Ponesimod	pipeline	MS	$ 486	$ 200
	JNJ-4528	pipeline	multiple myeloma	$ 1,100	$ -
	Cusatuzumab	pipeline	Cancer/AML	$ 306	$ -
	Niraparib	pipeline	Prostate cancer	$ 350	$ -
	Lazertinib/JNJ-1937	pipeline	Cancer EGFR	$ 396	$ -
	JNJ-7564	pipeline	Multiple myeloma	$ 270	$ -
	Amivantamab/JNJ-6372	pipeline	EGFR lung cancer	$ 396	$ -
	Aprocitentan	pipeline	Hypertension	$ 90	$ -
	AAV-RPGR/CNGB3	pipeline	Rare eye diseases	$ -	$ -
	JNJ-4500	pipeline	Crohn's and ulcerative colitis	$ 150	$ -
	Seltorexant/JNJ-7922	pipeline	Major depression	$ -	$ -
	Ad26.RSV.preF	pipeline	RSV	$ -	$ -
	Teclistamab/JNJ-7957	pipeline	Multiple myeloma	$ -	$ -
	BMS-986177	pipeline	-	$ -	$ -
Eli Lilly (LLY)					
	Forteo	expiring patents	osteoporosis	$ 463	$ 519
	Alimta	expiring patents	cancer	$ 786	$ 501
	Cialis	expiring patents	cardiovascular	$ 568	$ 374
	Humalog	expiring patents	diabetes	$ 2,518	$ 2,089
	Humulin	inline	diabetes	$ 1,260	$ 1,129
	Jardiance	inline	diabetes	$ 1,827	$ 1,927
	Trulicity	inline	diabetes	$ 6,384	$ 6,616
	Cyramza	inline	cancer	$ 1,309	$ 1,204
	Taltz	inline	immunology	$ 4,164	$ 2,908
	Basaglar	inline	diabetes	$ 1,497	$ 1,536
	Verzenio/Abemaciclib	inline	cancer	$ 2,612	$ 2,106
	Olumiant/Baricitinib	inline	RA	$ 1,529	$ 1,237
	Emgality/galcanezumab/LY2951742	inline	migraine/cluster headache	$ 1,211	$ 1,256
	Reyvow/Lasmiditan	inline	acute migraine	$ 535	$ 364
	Tanezumab	pipeline	pain	$ 632	$ 281
	Loxo-292	pipeline	cancer	$ 590	$ -
	Mirikizumab	pipeline	immunology	$ 775	$ 610
	Lebrikizumab	pipeline	Atopic Dermatitis	$ 900	$ 290
	Zagotenemab	pipeline	Alzheimer's	$ -	$ -
	Donanemab	pipeline	Alzheimer's	$ -	$ -
	Tirzepatide	pipeline	diabetes	$ 475	$ 1,088

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Merck (MRK)					
	Zetia/Vytorin	expiring patents	cholesterol lowering	$ 253	$ 257
	Remicade	expiring patents	immunology	$ 121	$ 121
	Januvia/Janumet	expiring patents	diabetes	$ 2,250	$ 1,284
	Keytruda	inline	cancer	$ 24,400	$ 21,534
	Gardasil	inline	HPV	$ 6,003	$ 5,810
	Lynparza	inline	cancer	$ 1,302	$ 1,216
	Lenvima	inline	cancer	$ 843	$ 1,018
	Steglatro	inline	diabetes	$ 494	$ 509
	Bridion	inline	Anesthesia reversal	$ 1,517	$ 1,369
	Pifeltro	inline	HIV	$ 162	$ 306
	V114	pipeline	Pneumococcal disease	$ 420	$ 593
	Gefapixant/MK-7264	pipeline	chronic cough	$ 173	$ 327
	V160	pipeline	CMV virus	$ -	$ 88
	MK-6482	pipeline	Cancer (rare mutations)	$ -	$ 108
	MK-8591	pipeline	HIV	$ 389	$ 726
Novartis (NVS)					
	Gleevec	expiring patents	cancer	$ 395	$ 466
	Lucentis	expiring patents	ophthalmology	$ 1,036	$ 1,104
	Afinitor	expiring patents	cancer	$ 214	$ 223
	Gilenya	expiring patents	MS	$ 808	$ 1,054
	Tasigna	inline	cancer	$ 531	$ 752
	Ilaris	inline	wide ranging	$ 1,992	$ 922
	Entresto	inline	cardiovascular	$ 1,971	$ 4,238
	Cosentyx	inline	immunology	$ 5,322	$ 5,608
	Kymriah	inline	cancer	$ 1,166	$ 1,030
	Kisqali	inline	cancer	$ 1,609	$ 1,407
	Xiidra	inline	dry eye	$ 571	$ 890
	Aimovig (erenumab)	inline	migraine	$ 720	$ 509
	Lutathera	inline	cancer	$ 543	$ 1,014
	Brolucizumab/RTH258	inline	AMD	$ 977	$ 1,186
	BAF312/siponimod	inline	MS	$ 930	$ 948
	Aleplisib BYL719	inline	cancer	$ 1,341	$ 1,319
	SEG101/crizanlizumab	inline	sickle cell anemia	$ 420	$ 647
	Zolgensma (AVXS-101)	inline	Spinal muscular atrophy (SMA)	$ 2,096	$ 2,035
	Capmatinib/INC280	pipeline	cancer	$ 300	$ 419
	QVM149	pipeline	asthma	$ 306	$ 281
	Inclisiran	pipeline	Cholesterol	$ 550	$ 1,097
	Ofatumumab/OMB157	pipeline	MS	$ 1,309	$ 1,742
	PDR001	pipeline	cancer	$ 144	$ -
	Lu-PSMA-617	pipeline	cancer	$ 570	$ 508
	Iscalimab/CFZ533	pipeline	transplant	$ -	$ -
	ABL001	pipeline	cancer	$ -	$ 166
	LNP023	pipeline	PNH and renal diseases	$ -	$ -
	Adriforant	pipeline	Moderate atopic dermatitis	$ -	$ -
	TQJ230/AKCEA-APO(a)-LRx	pipeline	Cardiovascular disease	$ -	$ -
	QGE031/ligelizumab	pipeline	hives	$ -	$ -

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Novo Nordisk (NVO)					
	Human Insulin	expiring patents	diabetes	DKK 6,900	-
	NovoRapid/NovoLog	expiring patents	diabetes	DKK 15,800	DKK 14,500
	NovoMix	expiring patents	diabetes	DKK 9,000	DKK 8,600
	Levemir	expiring patents	diabetes	DKK 5,200	DKK 5,200
	NovoSeven	expiring patents	hemophilia	DKK 6,100	DKK 5,600
	Norditropin	expiring patents	growth disorders	DKK 6,300	DKK 8,000
	Tresiba	inline	diabetes	DKK 12,100	DKK 11,700
	Victoza	inline	diabetes	DKK 8,300	DKK 7,700
	Ozempic	inline	diabetes	DKK 40,000	DKK 38,400
	Ryzodeg	inline	diabetes	DKK 1,700	DKK 2,300
	Xultophy	inline	diabetes	DKK 4,400	DKK 4,800
	Saxenda	inline	obesity	DKK 4,800	DKK 7,300
	Fiasp	inline	diabetes	DKK 2,700	DKK 3,600
	Rebinyn / Refixia (N9-GP)	inline	hemophilia	DKK 1,100	DKK 1,100
	N8-GP/NN7088 & NovoEight	pipeline	hemophilia	DKK 1,800	DKK 3,200
	Oral semaglutide	pipeline	diabetes	DKK 25,500	DKK 28,200
	Concizumab	pipeline	hemophilia	-	DKK 900
	LAI287 (insulin icodec)	pipeline	diabetes	DKK 1,800	-
	Injectable semaglutide	pipeline	NASH	DKK 2,600	-
	Injectable semaglutide	pipeline	obesity	DKK 5,100	DKK 5,200
Pfizer (PFE)					
	Lyrica	expiring patents	Fibromyalgia, neuropathic pain	$ 757	$ 752
	Enbrel	expiring patents	immunology	$ 710	$ 790
	Prevnar 13	inline	Streptococcus pneumoniae	$ 6,228	$ 6,210
	Ibrance	inline	Breast Cancer	$ 7,164	$ 8,767
	Xeljanz	inline	immunology	$ 3,487	$ 3,100
	Eliquis	inline	cardiovascular	$ 6,555	$ 6,536
	Bavencio	inline	cancer	$ 741	$ 526
	Steglatro	inline	diabetes	$ -	$ 344
	Xtandi	inline	prostate cancer	$ 1,260	$ 1,638
	Vizimpro/Dacomitinib	inline	cancer	$ 263	$ 339
	Daurismo/Glasdegib	inline	cancer	$ -	$ 347
	Lorbrena/Lorlatinib	inline	cancer	$ -	$ 361
	Talzenna/Talazoparib	inline	cancer	$ 402	$ 424
	Vyndaqel/Tafamidis	inline	cardiomyopathy	$ 2,179	$ 2,760
	Braftovi/Mektovi	inline	cancer	$ 1,876	$ 1,345
	Tanezumab	pipeline	pain	$ 665	$ 246
	Abrocitinib/PF-04965842	pipeline	atopic dermatitis	$ 700	$ 441
	Fidanacogene Elaparvovec	pipeline	hemophilia	$ -	$ 216
	PF-06651600	pipeline	immunology	$ 462	$ 238
	PF-06700841	pipeline	immunology	$ -	$ 11
	PF-06425090	pipeline	C. difficile	$ 750	$ -
	PF-06826647	pipeline	psoriasis and IBD	$ -	$ 7
	SB-525	pipeline	Hemophilia A	$ 300	$ -
	PF-06928316	pipeline	Respiratory Syncytial Virus (RSV)	$ -	$ 44

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Regeneron (REGN)					
	Eylea (aflibercept)	expiring patents	ophthalmology	$ 4,400	$ 5,000
	Praluent (alirocumab)	inline	cardiovascular	$ 400	$ 250
	Kevzara (sarilumab)	inline	immunology	$ 475	$ 550
	Dupixent (dupilumab)	inline	immunology	$ 7,100	$ 7,100
	Libtayo (cemiplimab/REGN2810)	inline	cancer	$ 600	$ 950
	Fasinumab (REGN475)	pipeline	pain	$ 290	$ -
	evinacumab	pipeline	Homozygous familial hypercholesterolemia	$ 150	$ 100
	garetosmab (REGN2477)	pipeline	FOP	$ 120	$ -
	REGN-COV2	pipeline	SARS-CoV-2	$2,000, 2021-22	-
	pozelimab (REGN3918)	pipeline	PNH and renal diseases	$ 100	$ -
	REGN5458/5459	pipeline	Multiple myeloma	$ 500	$ -
	REGN1979	pipeline	lymphoma	$ 540	$ 340
Roche (RHHBY)					
	Rituxan/Mabthera	expiring patents	oncology (NHL/CLL), arthritis	$ 2,700	$ 2,500
	Herceptin	expiring patents	HER2+ breast, gastric cancers	$ 3,300	$ 2,900
	Avastin	expiring patents	various oncology	$ 3,500	$ 3,000
	Esbriet	expiring patents	idiopathic pulmonary fibrosis (IPF)	$ 300	$ 600
	Xolair	expiring patents	asthma, hives	$ 1,300	$ 1,500
	Actemra/RoActemra	expiring patents	rheumatoid arthritis	$ 2,300	$ 2,600
	Gazyva	inline	oncology (NHL/CLL)	$ 1,800	$ 1,400
	Perjeta	inline	HER2+ breast cancer	$ 4,700	$ 5,500
	Tecentriq/atezolizumab	inline	cancer	$ 11,300	$ 6,400
	Venclexta/venetoclax, GDC/ABT-199	inline	hematological oncology	$ 2,900	$ 2,800
	Kadcyla	inline	HER2+ breast cancer	$ 1,900	$ 2,500
	Lucentis	inline	ophthalmology	$ 1,400	$ 1,200
	Alecensa/alectinib	inline	ALK-positive NSCLC	$ 1,600	$ 1,600
	Ocrevus/ocrelizumab	inline	RRMS/PPMS	$ 7,100	$ 6,700
	Hemlibra / emicizumab / ACE910 (RG6013)	inline	hemophilia	$ 4,400	$ 4,600
	Xofluza (baloxavir marboxil)	inline	influenza	$ 550	$ 500
	Polivy (polatuzumab vedotin)	inline	hematological oncology	$ 1,100	$ 1,200
	Rozlytrek (entrectinib)	inline	Pan-tumor ROS1 and NTRK fusions	$ 600	$ 450
	risdiplam	pipeline	Spinal muscular atrophy	$ 700	$ 1,300
	satralizumab	pipeline	Neuromyelitis optica	$ 350	$ 370
	etrolizumab	pipeline	Ulcerative colitis, Crohn's disease	$ 700	$ 650
	RG6042/HTT-ASO	pipeline	Huntington's disease	$ 225	$ 300
	idasanutlin	pipeline	hematological oncology	$ -	$ 50
	cibisatuzumab (RG7802)	pipeline	colorectal cancer, CEA-high cancers	$ 240	$ -
	ipatasertib	pipeline	TNBC, prostate cancer	$ 480	$ 650
	gantenerumab	pipeline	Alzheimer's disease	$ 350	$ 150
	RG6026 and mosunetuzumab	pipeline	hematological oncology	$ 390	$ 700
	SPK-8011/RG6357	pipeline	Hemophilia A	$ 400	$ -
	SRP-9001/RG6356	pipeline	Duchenne muscular dystrophy (DMD)	$ 100	$ 300
	GDC-0077/RG6114	pipeline	HER2-/HR+ breast cancer	$ 150	$ 120
	Tiragolumab/RG6058	pipeline	Oncology (lung cancer)	$ 500	$ 400
	RG6171/GDC-9545	pipeline	HER2-/HR+ breast cancer	$ 180	$ -
	faricimab	pipeline	ophthalmology	$ 225	$ 300

Source: Morningstar, DrugAnalyst consensus, and company reports.

Firm (Ticker)	Drug	Category	Therapeutic Area	2024E Sales, Morningstar	2024E Sales, Consensus
Sanofi (SNY)					
	Lantus	expiring patents	diabetes	€ 1,888	€ 1,736
	Plavix	expiring patents	cardiovascular	€ 805	€ 774
	Lovenox	expiring patents	deep vein thrombosis	€ 983	€ 1,046
	Aubagio	inline	MS	€ 508	€ 663
	Toujeo	inline	diabetes	€ 1,189	€ 1,007
	Praluent	inline	cholesterol lowering	€ 370	€ 331
	Kevzara/Sarilumab	inline	immunology	€ 348	€ 562
	Dupixent/dupilumab	inline	immunology	€ 6,865	€ 7,147
	Admelog/SAR342434	inline	diabetes	€ 200	€ 343
	Libtayo/Cemiplimab/REGN2810	inline	cancer	€ 346	€ 302
	Cablivi/Caplacizumab	inline	aTTP	€ 427	€ 442
	Isatuximab	pipeline	blood cancer	€ 291	€ 494
	Sutimlimab	pipeline	cold agglutinin disease	€ 173	€ 366
	Avalglucosidase alfa	pipeline	Pompe Disease	-	-
	SERD-859	pipeline	Breast cancer	€ 313	-
	BIV001	pipeline	Hemophilia A	-	-
	Venglustat	pipeline	Rare diseases	€ 225	€ 125
	Nirsevimab	pipeline	RSV prevention	€ 50	€ 120
	SAR442168	pipeline	MS	-	-
	Fitusiran	pipeline	hemophilia	€ 385	€ 309

Source: Morningstar, DrugAnalyst consensus, and company reports.

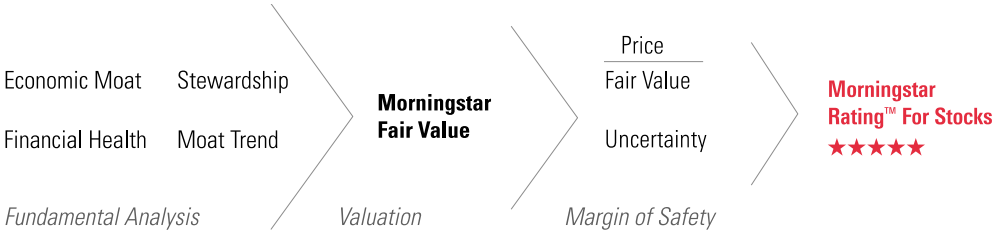
Research Methodology for Valuing Companies

Overview

At the heart of our valuation system is a detailed projection of a company's future cash flows, resulting from our analysts' research. Analysts create custom industry and company assumptions to feed income statement, balance sheet, and capital investment assumptions into our globally standardized, proprietary discounted cash flow, or DCF, modeling templates. We use scenario analysis, in-depth competitive advantage analysis, and a variety of other analytical tools to augment this process. Moreover, we think analyzing valuation through discounted cash flows presents a better lens for viewing cyclical companies, high-growth firms, businesses with finite lives (e.g., mines), or companies expected to generate negative earnings over the next few years. That said, we don't dismiss multiples altogether but rather use them as supporting cross-checks for our DCF-based fair value estimates. We also acknowledge that DCF models offer their own challenges (including a potential proliferation of estimated inputs and the possibility that the method may miss short-term market price movements), but we believe these negatives are mitigated by deep analysis and our long-term approach.

Morningstar's equity research group ("we," "our") believes that a company's intrinsic worth results from the future cash flows it can generate. The Morningstar Rating for stocks identifies stocks trading at a discount or premium to their intrinsic worth—or fair value estimate, in Morningstar terminology. Five-star stocks sell for the biggest risk-adjusted discount to their fair values, whereas 1-star stocks trade at premiums to their intrinsic worth.

Morningstar Research Methodology



Source: Morningstar.

Four key components drive the Morningstar rating: (1) our assessment of the firm's economic moat, (2) our estimate of the stock's fair value, (3) our uncertainty around that fair value estimate, and (4) the current market price. This process ultimately culminates in our single-point star rating.

Economic Moat

The concept of an economic moat plays a vital role not only in our qualitative assessment of a firm's long-term investment potential, but also in the actual calculation of our fair value estimates. An economic moat is a structural feature that allows a firm to sustain excess profits over a long period of time. We define economic profits as returns on invested capital (ROIC) over and above our estimate of a firm's cost of capital, or weighted average cost of capital (WACC). Without a moat, profits are more susceptible to competition. We have identified five sources of economic moats: intangible assets, switching costs, network effect, cost advantage, and efficient scale.

Companies with a narrow moat are those we believe are more likely than not to achieve normalized excess returns for at least the next 10 years. Wide-moat companies are those in which we have very high confidence that excess returns will remain for 10 years, with excess returns more likely than not to remain for at least 20 years. The longer a firm generates economic profits, the higher its intrinsic value. We believe low-quality, no-moat companies will see their normalized returns gravitate toward their cost of capital more quickly than companies with moats.

To assess the sustainability of excess profits, analysts perform ongoing assessments of the moat trend. A firm's moat trend is positive in cases where we think its sources of competitive advantage are growing stronger, stable where we don't anticipate changes to competitive advantages over the next several years, or negative where we see signs of deterioration.

Estimated Fair Value

Combining our analysts' financial forecasts with the firm's economic moat helps us assess how long returns on invested capital are likely to exceed the firm's cost of capital. Returns of firms with a wide economic moat rating are assumed to fade to the perpetuity period over a longer period of time than the returns of narrow-moat firms, and both will fade slower than no-moat firms, increasing our estimate of their intrinsic value.

Our model is divided into three distinct stages:

Stage I: Explicit Forecast

In this stage, which can last 5 to 10 years, analysts make full financial statement forecasts, including items such as revenue, profit margins, tax rates, changes in working capital accounts, and capital spending. Based on these projections, we calculate earnings before interest, after taxes (EBI) and net new investment (NNI) to derive our annual free cash flow forecast.

Stage II: Fade

The second stage of our model is the period it will take the company's return on new invested capital—the return on capital of the next dollar invested (RONIC)—to decline (or rise) to its cost of capital. During the Stage II period, we use a formula to approximate cash flows in lieu of explicitly modeling the income statement, balance sheet, and cash flow statement as we do in Stage I. The length of the second stage depends on the strength of the company's economic moat. We forecast this period to last anywhere from one year (for companies with no economic moat) to 10–15 years or more (for wide-moat companies). During this period, cash flows are forecast using four assumptions: an average growth rate for EBI over the period, a normalized investment rate, average return on new invested capital (RONIC), and the number of years until perpetuity, when excess returns cease. The investment rate and return on new invested capital decline until a perpetuity value is calculated. In the case of firms that do not earn their cost of capital, we assume marginal ROICs rise to the firm's cost of capital (usually attributable to less reinvestment), and we may truncate the second stage.

Stage III: Perpetuity

Once a company's marginal ROIC hits its cost of capital, we calculate a continuing value, using a standard perpetuity formula. At perpetuity, we assume that any growth or decline or investment in the business neither creates nor destroys value and that any new investment provides a return in line with estimated WACC.

Because a dollar earned today is worth more than a dollar earned tomorrow, we discount our projections of cash flows in stages I, II, and III to arrive at a total present value of expected future cash flows. Because we are modeling free cash flow to the firm—representing cash available to provide a return to all capital providers—we discount future cash flows using the WACC, which is a weighted average of the costs of equity, debt, and preferred stock (and any other funding sources), using expected future proportionate long-term, market value weights.

Uncertainty Around That Fair Value Estimate

Morningstar's uncertainty rating captures a range of likely potential intrinsic values for a company and uses it to assign the margin of safety required before investing, which in turn explicitly drives our stock star rating system. The uncertainty rating represents the analysts' ability to bound the estimated value of the shares in a company around the fair value estimate, based on the characteristics of the business underlying the stock, including operating and financial leverage, sales sensitivity to the overall economy, product concentration, pricing power, and other company-specific factors.

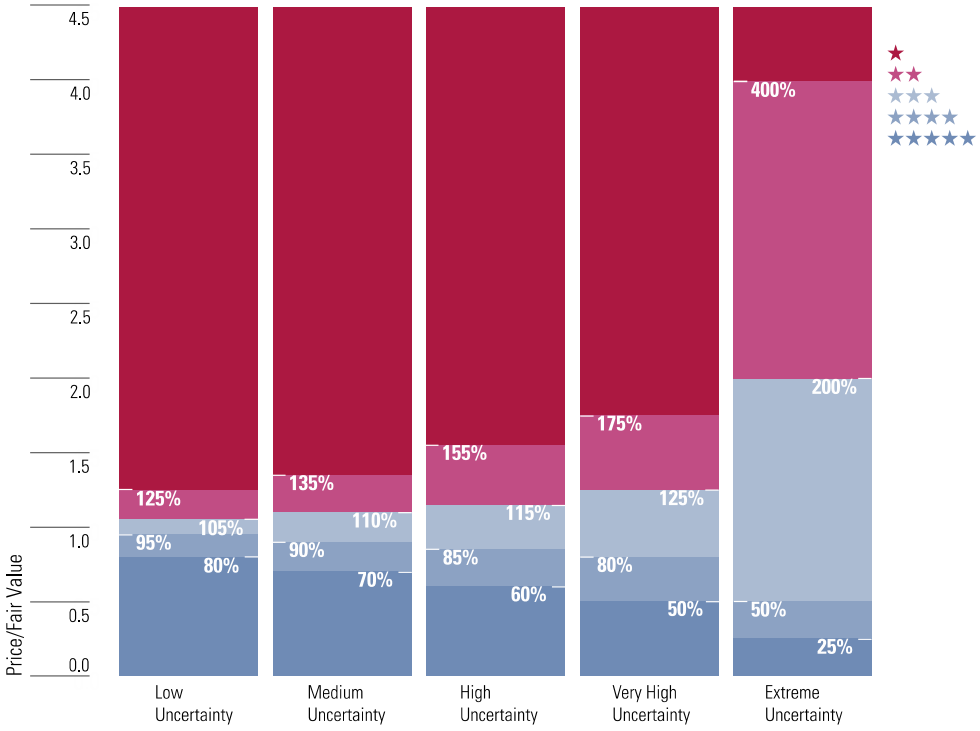
Analysts consider at least two scenarios in addition to their base case: a bull case and a bear case. Assumptions are chosen such that the analyst believes there is a 25% probability that the company will perform better than the bull case and a 25% probability that the company will perform worse than the bear case. The distance between the bull and bear cases is an important indicator of the uncertainty underlying the fair value estimate.

Our recommended margin of safety widens as our uncertainty regarding the estimated value of the equity increases. The more uncertain we are about the estimated value of the equity, the greater the discount we require relative to our estimate of the value of the firm before we would recommend the purchase of the shares. In addition, the uncertainty rating provides guidance in portfolio construction based on risk tolerance.

Our uncertainty ratings for our qualitative analysis are low, medium, high, very high, and extreme.

- Low: Margin of safety for 5-star rating is a 20% discount and for 1-star rating is a 25% premium.
- Medium: Margin of safety for 5-star rating is a 30% discount and for 1-star rating is a 35% premium.
- High: Margin of safety for 5-star rating is a 40% discount and for 1-star rating is a 55% premium.
- Very high: Margin of safety for 5-star rating is a 50% discount and for 1-star rating is a 75% premium.
- Extreme: Margin of safety for 5-star rating is a 75% discount and for 1-star rating is a 300% premium.

Morningstar Equity Research Star Rating Methodology



Market Price

The market prices used in this analysis and noted in the report come from the exchange on which the stock is listed, which we believe is a reliable source.

For more details about our methodology, please go to https://shareholders.morningstar.com.

Morningstar Star Rating for Stocks

Once we determine the fair value estimate of a stock, we compare it with the stock's current market price on a daily basis, and the star rating is automatically recalculated at the market close on every day the market on which the stock is listed is open. Our analysts keep close tabs on the companies they follow and, based on thorough and ongoing analysis, raise or lower their fair value estimates as warranted.

Please note, there is no predefined distribution of stars. That is, the percentage of stocks that earn 5 stars can fluctuate daily, so the star ratings, in the aggregate, can serve as a gauge of the broader market's valuation. When there are many 5-star stocks, the stock market as a whole is more undervalued, in our opinion, than when very few companies garner our highest rating.

We expect that if our base-case assumptions are true, the market price will converge on our fair value estimate over time, generally within three years (although it is impossible to predict the exact time frame in which market prices may adjust).

Our star ratings are guideposts to a broad audience, and individuals must consider their own specific investment goals, risk tolerance, tax situation, time horizon, income needs, and complete investment portfolio, among other factors.

The Morningstar Star Ratings for stocks are defined below:

★★★★★ We believe appreciation beyond a fair risk-adjusted return is highly likely over a multiyear time frame. Scenario analysis developed by our analysts indicates that the current market price represents an excessively pessimistic outlook, limiting downside risk and maximizing upside potential.

★★★★ We believe appreciation beyond a fair risk-adjusted return is likely.

★★★ Indicates our belief that investors are likely to receive a fair risk-adjusted return (approximately cost of equity).

★★ We believe investors are likely to receive a less than fair risk-adjusted return.

★ Indicates a high probability of undesirable risk-adjusted returns from the current market price over a multiyear time frame, based on our analysis. Scenario analysis by our analysts indicates that the market is pricing in an excessively optimistic outlook, limiting upside potential and leaving the investor exposed to capital loss.

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