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Yescarta sales flatten as Kite buy written down

Gilead Writes Down Kite Buy As Yescarta Sales Flatten Out

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Perhaps one of the most interesting aspects of Gilead Sciences Inc.'s fourth quarter and full-year 2019 earnings call on 4 February was what the company did not talk about – an $800m pre-tax impairment charge it took in the fourth quarter related to its acquisition of Kite Pharma Inc. While the lymphoma treatment Yescarta, the centerpiece of the deal, posted flat quarter-over-quarter sales growth, mentions of Kite were scant during the hour-plus call.

Earlier this year, CEO Daniel O'Day spoke about Gilead's potential to develop new growth-driving products through both internal and external innovation at the J.P. Morgan Healthcare Conference. *(Also see "J.P. Morgan Notebook Day 1: No Big Deals, But Plenty Of Pipeline, Commercial Highlights" - Scrip, 14 Jan, 2020.)* Returning to that theme during the earnings call, O'Day talked up the promise of Gilead's partnership with Galapagos NV, including the potential for approval of JAK1 inhibitor filgotinib in rheumatoid arthritis and upcoming Phase III data with that compound in ulcerative colitis.

The company hopes filgotinib will be a best-in-class JAK inhibitor in RA – it has an August action date at the US Food and Drug Administration and also is under review in Europe and Japan. *(Also see "Gilead Hopes Selectivity Will Ease Safety Labeling For Filgotinib" - Scrip, 25 Oct, 2019.)*

Chief financial officer Andrew Dickinson reported that Yescarta (axicabtagene ciloleucel) brought in $122m globally during the fourth quarter, rising just 3% sequentially from $118m in the third quarter, which fell from $120m in the second quarter. Despite the recent flattening, fourth quarter Yescarta sales were up 51% from Q4 2018.

"The year-over-year increase was driven by a higher number of therapies provided to patients and its continued expansion in Europe," Dickinson said. Full-year sales of Yescarta were $456m, roughly double the $264m posted in 2018, with $373m of sales in the US and $83m ex-US.

O'Day said last May, during his first quarterly earnings call as Gilead CEO, that the company planned to make Kite a separate business entity within Gilead with its own CEO, perhaps indicating a declining role in the Foster City, CA-based firm's plans for growth. *(Also see "Gilead To Let Kite Fly Free; O'Day Says It Will Become Separate Business Unit" - Scrip, 2 May, 2019.)*

On the 4 February call, O'Day said Gilead looks forward to presenting Phase III data for Yescarta in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients during the second half of 2020, and also cited a second Kite candidate, KTE-X19, as under review in the US and EU for relapsed/refractory mantle cell lymphoma.

The CEO did not mention the $800m write-down, however, which followed an $820m write-down of the Kite transaction during 2018. *(Also see "Gilead Maintains Optimistic Outlook For Yescarta Despite Slow Growth" - Scrip, 4 Feb, 2019.)* Recently appointed chief medical officer Merdad Persay pointed out in his overview of Gilead's R&D pipeline that the company has 15 oncology candidates in clinical development, citing "a broad portfolio, including Kite." *(Also see "Gilead's New O'Day Regime Has New R&D Structure " - Scrip, 10 Oct, 2019.)*

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from the editor

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Welcome to our Valentine's issue. We're not going to mark the day with heart motifs or romantic suggestions (sorry). But the key to a good relationship is listening attentively to each other, and we want to be a good partner in this regard.

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Regeneron Wades Deeper Into Oncology With Ambitions To Be A Force In The Space

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Regeneron Pharmaceuticals Inc. – best known for its antibody drug development platform and commercial success with Eylea (aflibercept) – is pivoting increasingly toward oncology. The company has one cancer drug on the market, the PD-1 inhibitor Libtayo (cemiplimab) in partnership with Sanofi, but behind it are a maturing pipeline of bispecific antibodies that Regeneron hopes will catapult the company into a serious oncology player.

The year 2020 will be an important one for Regeneron in that regard, with several clinical trial milestones that could indicate how successfully Regeneron will execute on this goal.

"We are starting to become known as an oncology company," senior VP-global clinical development David Weinreich said in an interview. *Scrip* talked to Weinreich at the J.P. Morgan Healthcare conference in January about the company's growing ambitions in oncology, the opportunity to leapfrog through combinations and balancing the investment-intensive therapeutic area with research in other areas.

"The history tells us it is not going to be any single drug," Weinreich said of the oncology development space. "It is going to be some combination, and that is where we are trying to position ourselves."

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To read the rest of this story go to: https://bit.ly/2UARVG5

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The Yescarta sales came in below Jefferies' projection for the quarter of $135m and Credit Suisse's expectation of $138m, as well as a $129m consensus estimate given by Credit Suisse analyst Evan Seigerman in a 4 February note.

HIV FRANCHISE SETS NEW QUARTERLY, ANNUAL SALES PEAKS

Overall, Gilead reported fourth quarter revenue of $5.8bn, up slightly from $5.7bn a year earlier, and full-year sales of $22.1bn, compared to $21.7bn in 2018. O'Day emphasized the strength of the company's core business, noting that the HIV franchise had once again set quarterly and annual sales records. *(Also see "O'Day Lays Out Plan For Gilead's Continued HIV Dominance" - Scrip, 14 Jan, 2020.)*

On the quarter, HIV sales of $4.6bn were up 9% year-over-year, according to chief commercial officer Johanna Mercier, while the annual total of $16.4bn accounted for a 12% increase over 2018.

"Today, approximately 80% of people living with HIV who are on therapy in the US are on a Gilead-based regimen," O'Day said. "Across the franchise, we've seen durability and sustainability of the business, which we expect to continue in 2020 and beyond."

He noted that much of the strength is being driven by Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide (TAF)) and said that about one in two patients who are new to therapy and patients who are switching therapy are initiating treatment with Biktarvy.

"We're also very pleased with the early progress with Descovy (emtricitabine/TAF) for PrEP [pre-exposure prophylaxis]," O'Day said.

Biktarvy yielded sales of $1.57bn during the fourth quarter, nearly $1.36bn of that in the US, up 23% from the prior quarter. Full-year sales of $4.74bn more than quadrupled the $1.18bn realized in 2018. Biktarvy now is on the market in 29 EU markets, Mercier said, and is the number-one HIV therapy in Germany, France, Spain and Italy. Overall, Gilead's quarterly HIV sales in Europe rose 10% year-over-year, she added.

Descovy brought in $437m worldwide during the quarter, and $1.5bn for the year. Mercier noted that 27% of US PrEP patients now take Descovy and Gilead expects to realize its goal of a 40%-45% market share in PrEP by the end of 2020.

For 2020, Gilead offered full-year product sales guidance of $21.8bn to $22.2bn, basically flat compared to 2019's performance. O'Day said that while HIV is robust and continues to grow, there are headwinds Gilead has to factor in, including the US patent expiration of Descovy predecessor Truvada (emtricitabine/tenofovir disoproxil fumarate) in 2021. Truvada yielded $2.81bn in sales during 2019, including $768m in the fourth quarter, nearly all of it in the US.

A current drag on performance is generic erosion in the cardiovascular franchise. Mercier pointed out that recent generic competition has decreased sales of angina drug Ranexa (ranolazine) by 90% and pulmonary arterial hypertension drug Letairis (ambrisentan) by 65%. That trend is expected to continue in 2020, she said. Gilead did not break out individual sales of either product in its report.

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Merck To Spin Out A New Company, Following Industry's Downsizing Trend

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Big pharma is getting smaller and more focused, not bigger, and now Merck & Co. Inc. is the latest company to announce that it will spin out its more mature pharmaceutical products. Merck announced on 5 February that it will spin off its women's health, legacy brands and biosimilars into a new publicly traded company.

Merck will remain focused on its high-growth drivers: oncology – namely the PD-1 inhibitor Keytruda (pembrolizumab), vaccines, hospital and animal health businesses.

"It is this purposeful shift coupled with greater prioritization and focus on key growth drivers that has led to the unprecedented growth that we are now experiencing," CEO Ken Frazier said during a same-day conference call announcing the spin out and 2019 financial results.

"Going forward, we see even greater opportunities to invest behind our innovative growth drivers in placing greater focus and prioritization behind these products, we must also think carefully about how to make the best possible use of the remainder of our expansive Human Health portfolio, which is comprised of more than 160 products in total," he said.

TWO DISTINCT PORTFOLIOS

Merck will retain brands like Keytruda, Lynparza (olaparib), Lenvima (lenvatinib mesylate), Gardasil (human papilloma virus vaccine), Bridion (sugammadex), Zerbaxa (ceftolozone/tazobactam) and Bravecto (fluralaner) and its diabetes business, including Januvia (sitagliptin). Merck will remain by far the larger company; the firm forecasts 2020 revenues to be between $48.8bn and $50.3bn.

Products that will be shifted to the new company represent about $6.5bn of 2020 forecasts. The separated entity's strategic vision will include becoming a leader in women's health. The portfolio will include women's health products like the Nexplanon (etonogestrel implant) contraceptive and fertility drugs; off-patent products in dermatology, pain, respiratory and cardiovascular disease, including Zetia (ezetimibe) and Vytorin (ezetimibe/simvastatin); and biosimilars, including Renflexis (infliximab-abda), Brenzys (etanercept) and Ontruzant (trastuzumab). Those three biosimilars generated $250m in 2019.

Nexplanon grew 12% to $787m in 2019 and, according to Merck, is the leading implantable, long-acting contraceptive in the US, with patent protection through 2027. "We expect Nexplanon to

be our first billion-dollar women's health product," said Kevin Ali, the CEO designate for the new company. The new portfolio will also contain the Nuvaring contraceptive, but that product began facing generic competition in the US in the last quarter of 2019.

The new company – which is yet to be named – will be "well positioned to capitalize on the highly fragmented women's health market," Ali added, with ambitions to grow both organically and through business development.

Most of the company's sales will be generated outside the US (approximately 75%) and the firm will have significant geographic reach. It will employ 10,000 to 11,000 employees and be headquartered in New Jersey.

The new company is expected to generate 2021 base-year revenues of $6bn-$6.5bn, lower than 2020 due to patent expirations, and a non-GAAP operating margin around 35% in the first year post separation, reflecting the costs of setting up a standalone business.

The new company will achieve low single-digit revenue growth, more than had been expected within Merck, Ali said. Earnings before interest, taxes, depreciation and amortization (EBITDA) margins are expected to be in the low-to-mid 40% range in the first year post-separation and increase over time. The company will have $8.5bn to $9.5bn in debt, with ample cash flow for potential business development or for paying down debt, as well as providing a dividend.

Spinning out the business will result in cost savings for Merck. For example, while the new company represents about 15% of Merck's human health revenues, based on 2020 forecasts, it consumes a larger share of operations. Merck said the separation will reduce its manufacturing footprint by 25% and reduce the number of products it sells by 50%.

"As a result, there will be a more optimized operating model. Merck will achieve even higher operating margins over time, creating additional headroom to invest in innovation," chief financial officer Robert Davies said.

Merck expects to achieve incremental operating efficiencies of more than $1.5bn by 2024 as a result, while continuing to increase investment in key growth drivers and pipeline assets. Merck is targeting non-GAAP operating margins greater than 40% in 2024, higher than previously forecast.

One of the challenges for Merck is that the spinout will increase its dependence on Keytruda, the mega blockbuster on which it is already highly dependent for growth.

FOLLOWING AN INDUSTRY TREND QUICKLY

Merck's effort to get smaller follows a growing industry trend among big pharmas to focus on select therapeutic areas and high-growth innovative brands. But Merck's decision to spin out part of the company came as a bit of a surprise. Pfizer Inc. spent nearly 10 years debating the merits of a split and preparing investors for it, before announcing last year that it will spin out its Upjohn legacy business to merge with Mylan NV into a new company to be called Viatris. Pfizer also carved out its consumer health care business into a new joint venture with GlaxoSmithKline PLC. GSK, on

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5 February, said it is planning a separation of the consumer health care business and the creation of two companies, but said it would take about three years to complete.

Merck's seemingly sudden decision to spin out part of the business raises some questions about how the company might think about using the profits from the transaction, which it expects to complete in the first half of 2021. The company said it expects to receive $8bn-$9bn through a special tax-free dividend from the new company, which it will allocate to business development or share repurchases.

Frazier said Merck has been considering breaking up the business for some time, however. "From our standpoint, this is the right time," he said. "A few years ago, when we were looking at this, we saw the opportunity but, for example, the cash flow generation of our legacy products was being employed at that time and standing up our oncology business, which we grew from the ground up."

TAPPING AN EXPERIENCED LEADERSHIP TEAM

The CEO of the new company, Ali, is a longtime veteran of Merck who most recently led the company's enterprise portfolio strategy initiative, reporting to Frazier. He previously was president-MSD international; president-emerging markets; senior VP in charge of the bone, respiratory, immunology and dermatology franchise; managing director of Germany and managing director of Turkey.

"Kevin has a proven track record of leadership at Merck with deep experience in global pharmaceutical markets and diverse therapeutic areas," Frazier said. "We're confident NewCo will be in capable and experienced hands with this leadership team.

The company's chairman will be Carrie Cox, who was chairman of Array BioPharma Inc., CEO and chairman of Humacyte Inc. and president of global pharmaceuticals at Schering-Plough Corp. before its acquisition by Merck in 2009.

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Merck: It's Not Just Keytruda Driving Future Growth: **https://bit.ly/37b2LoJ**

Pharma Is Priority As GSK Confirms Split With Consumer

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GlaxoSmithKline PLC has begun its two-year program to split into two, creating a consumer healthcare standalone and a "biopharma company focused on science related to the immune system, use of genetics and new technologies."

There had been some conflicting messages of late regarding the future of the consumer business which GSK operates as a joint venture with Pfizer since a deal that closed at the end of July last year. At the J.P. Morgan Healthcare Conference in January, Pfizer CEO Albert Bourla said he believed the JV was moving towards an initial public offering within three to four years but GSK, which has majority ownership (68%) of the JV, also has control of the separation and is looking to move faster. *(Also see "No More 'Major' Deals For GSK Consumer Before IPO – CEO Walmsley " - HBW Insight, 15 Jan, 2020.)*

Speaking as GSK unveiled a decent if unspectacular set of financials for the full year and fourth quarter, CEO Emma Walmsley noted that the company was hopeful of completing the separation three years from the July 2019 closing of the JV. Building the technical infrastructure and corporate functions needed to prepare the consumer healthcare unit to stand alone will result in £600-£700m one-time costs; the separation program will target £700m in annual savings by 2022, with total costs estimated at £2.4bn.

Walmsley stated that "our first priority remains, as I said many times, to invest in R&D and future growth drivers." Recent data readouts "underpin our decision to further increase investment in R&D and these new products."

The separation program, referred to internally at GSK as 'Future Ready', will act as "a unique catalyst to reset the capabilities and cost bases for both companies," she added. One part of this will be to divest non-core assets and raise R&D funds for "the new GSK" and a number of them are under review, she noted.

The first to go is likely to be GSK's prescription dermatology business. Chief financial officer Iain Mackay said that division had revenues of £200-300m, noting, "It's a good business, not a priority business for us but we certainly believe it's a prospect…for other people."

GSK is also looking at the sale of a number of the equity holdings it has in other companies which "represents an interesting opportunity for us to reprioritize capital allocation towards the growth drivers within the organization," he added. Divestment proceeds should be in the region of £1.6bn, more than enough to cover the cash costs of the separation program, he added.

SHINGRIX IN DEMAND

As for the fourth quarter financials, which saw revenues rise 11% to £8.90bn and adjusted operating profit slide 11% to £1.85bn, the shingles vaccine Shingrix caught the eye, with sales reaching £532m. Walmsley noted that 14 million people in the US have been vaccinated with at least one dose, "and plenty of opportu-

GSK's Q4 Sales By Segment

THERAPEUTIC AREA	Q4 SALES £M	% (CER)
Established pharma	2,173	-14
HIV	1,257	0
Respiratory	892	+9
Immuno-inflammation	170	+26
Oncology	66	N/A
Vaccines	1,742	+21

Source: GSK.

nity remains." Shingrix was approved in May 2019 in China "where we're planning a phased introduction later this year," she said, adding that "our capacity expansion plans for this transformative product in our portfolio are making good progress."

However, heavy demand for the vaccine is still causing shortages of supply. Mackay said that "we see limited opportunity for further growth beyond 2020 until we bring our new facility online, which we don't expect before 2024."

GSK also spoke about its return to oncology but there is a lot of ground to make up. The company spent over $5.1bn to buy Tesaro, and its PARP inhibitor Zejula, (niraparib) but sales of the drug which is approved for ovarian cancer patients in the second-line maintenance setting remain luckluster, bringing in just £66m in the fourth quarter. *(Also see "GSK Gears Up For Three Cancer Launches In 2020" - Scrip, 5 Nov, 2019.)*

However R&D head Hal Barron highlighted the PRIMA data presented at the European Society for Medical Oncology meeting in Barcelona in September which he claimed demonstrated the value of monotherapy of Zejula for all-comers, not just in patients with BRCA mutations, when given in the frontline setting as maintenance therapy. He said that enrolment has started for the pivotal MOONSTONE study investigating Zejula plus the investigational PD-1 inhibitor dostarlimab for platinum-resistant ovarian cancer patients which will read out in 2021 and "together, we believe these data will help establish Zejula as the most compelling PARP inhibitor for women with ovarian cancer." *(Also see "New Front Opens in First-Line Ovarian Cancer Market: GSK's Zejula Vs. AZ's Lynparza " - Scrip, 29 Sep, 2019.)*

In addition, given Zejula's "unique pharmacokinetic profile, including its ability to penetrate the blood-brain barrier, we plan to initiate one or two pivotal studies in patients with lung and/or breast cancer by year-end," Barron added.

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GSK Has High Hopes For COPD Vaccine: **https://bit.ly/2SCm6Ka**

Roche Has Blockbusters In Its Pipeline – But Demurs On Predicting Hits

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Biosimilars will take a bigger bite out of Roche's revenues in 2020 but the year should also see multiple hits from a broad pipeline – though CEO Severin Schwan and pharma head Bill Anderson do not want to make any bold predictions about surprise wins.

Roche managed to ride out the beginnings of a biosimilar attack last year on its big three cancer blockbusters, Avastin, Herceptin and Rituxan/MabThera.

But 2020 will see biosimilars land a much bigger blow: they are expected to snatch a full CHF4bn ($4.12bn) in revenues from the firm.

Biosimilar challengers to Avastin and Herceptin were launched last year in the US, but will only gain real momentum and market share as 2020 progresses, deepening the CHF1.3bn erosion seen last year, largely due to biosimilars in Europe.

CEO Severin Schwan and the Roche leadership team presented this outlook at a 2019 results meeting with analysts in London on 30 January, but were still able to forecast revenue growth in 2020, albeit a more modest number than the 9% achieved last year.

Leading that growth are a trio of new, fast-growing blockbusters: multiple sclerosis drug Ocrevus (ocrelizumab), hemophilia treatment Hemlibra (emicizumab) and immunotherapy Tecentriq (atezolizumab), which between them generated nearly CHF7bn revenues last year. These will sustain Roche's momentum this year, but the Swiss pharma company also has one of the best late-stage pipelines in the sector, with an exceptional number of approvals and pivotal read-outs expected throughout 2020.

STAND-OUTS STILL HARD TO PREDICT

These range from some near certainties for approval – such as the Tecentriq + Avastin combination in liver cancer – to "Hail Marys" such as its Alzheimer's candidate gantenerumab.

Another major launch this year which looks certain to have a major impact is risdiplam, an oral treatment for spinal muscular atrophy (SMA), which is aiming to seize market share from Biogen's Spinraza (nusinersen) and Novartis's Zolgensma (onasemnogene abeparvovec).

Probably the biggest "binary catalyst" this year are the Phase III read-outs from etrolizumab, a new ulcerative colitis (UC) treatment which Roche believes can surpass the current standard of care, with analysts predicting peak annual sales of around $3bn (see table on page 8).

Nevertheless, UC is a therapy area strewn with late-stage failures over the last decade, so etrolizumab's success is far from certain. It has a string of late-stage trial readouts (including head-to-head studies with Humira (adalimumab) and Remicade (infliximab) and a US FDA filing scheduled for 2020. In the longer term, it must also show some advantages over

Roche's Next Blockbuster Candidates

Roche has an exceptional number of regulatory decisions and pivotal read-outs in 2020

CANDIDATE	INDICATION	MARKET POTENTIAL	CATALYST
Tecentriq+Avastin	Hepatocellular carcinoma cancer (HCC)	$1.5bn	US approval + launch anticipated H1 2020
Ipatasertib	HR+ breast cancer, TNBC and prostate cancer	$1bn	Three Phase III readouts in 2020E, filings in TNBC, colorectal cancer
Etrolizumab	Ulcerative colitis	$3bn	Phase III results from Humira, Remicade head-to-heads, FDA filing
Risdiplam	Spinal muscular atrophy (SMA) types 1-3	$2bn	FDA approval anticipated by 24 May 2020
Polivy	First-line aggressive lymphoma (DLBCL)	$1.3bn	Phase III POLARIX - year end 2020/Q1 2021
Lucentis Port Delivery System	Neovascular age-related macular degeneration (nAMD)	$1bn	ARCHWAY Phase III results expected mid 2020
Faricimab	Diabetic macular edema	$1bn	Phase III Q4 2020

Market potential sources: Jefferies, Deutsche Bank

Takeda's Entyvio (vedolizumab), already a near-$4bn blockbuster in the therapy area.

Entyvio targets alpha(4) beta(7) integrin whereas etrolizumab hits alpha(4) beta(7) plus another integrin, alpha E beta 7, and Roche hope this dual mechanism will prove clinically significant in clinical trials.

Analysts are always looking for clues from management about where any potential upsides might appear in the pipeline, and at the London meeting CEO Severin Schwan and pharma division head Bill Anderson took time to muse about the nature of R&D success – and its continuing unpredictability.

Anderson was, not surprisingly, upbeat about prospects for the latest crop of drugs, but would not be drawn too far on predictions. "I haven't been very good at predicting the uptake," he said.

"I knew Ocrevus was going to be really big but Hemlibra has surpassed all the market research we did. Normally you do market research and then you adjust it down because market research [has] sort of a bias [because] you're asking about this thing. But with Hemlibra, the actual uptake has far surpassed the market research."

On etrolizumab, Anderson said the clinical and commercial profile of rival Entyvio was a good indicator that its challenger would succeed, but nevertheless cautioned on high failure rates in Phase III trials in UC.

Roche is hoping its once-a-month subcutaneous formulation with an autoinjector will make it more appealing to patients and doctors compared with Entyvio, which must be administered via an infusion every eight weeks.

Severin Schwan joined the discussion, saying Roche's success rate in Phase III trials in recent years had been around 66% - in other words two successes for every failure. He said Roche experienced this problem in 2010, when it suffered multiple late-stage disappointments, including diabetes therapy taspoglutide and several antibody-drug conjugates which had to be abandoned.

Schwann recalled: "All our growth expectations turned into actually a decline of sales. So you can have a scenario like that, and then you have times when kind of everything works; I've seen these phases as well."

He concluded: "Look at the growth which we had in 2019… at the end of the day, it is basically three medicines which have made the difference. So just imagine if all three of them would have failed. It would have been a very different space. And we can't get rid of this binary situation in our industry, it remains high risk, and high opportunity."

Analysts continue to rate Roche's strategy highly among the big pharma players, and it continues to please shareholders – this year planning to increase its dividend, as it has for a remarkable 33 years in a row.

There are plenty of headwinds that could hold it back in 2020, such as a faster than expected encroachment of biosimilars or a slowdown in sales of its rising stars, or indeed pipeline failures.

The company began the year with one trial disappointment – the failure of Tecentriq in adjuvant bladder cancer – though this was not one of the most prized niches for the immunotherapy (IO) and one which does not signify similar obstacles in adjuvant settings in other tumor types.

More significant IO readouts will come this year – including in a new first-line melanoma combination, and in adjuvant and neoaduvant lung cancer. Meanwhile in triple-negative breast cancer (TNBC), where Tecentriq has the lead, Merck & Co. Inc. could close the gap with its KEYNOTE-355 trial, reading out later this year.

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BMS Earnings Beat Estimates, But Opdivo Sales Slide Continues

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Bristol-Myers Squibb Co. reported its third consecutive quarter of declining Opdivo (nivolumab) sales in the US, and second consecutive quarterly sales decline globally, on 6 February. As a result, executives spent most of the company's earnings call explaining that Bristol-Myers expects its PD-1 inhibitor to return to growth through new indications before Revlimid (lenalidomide) – acquired in the recently closed $76bn acquisition of Celgene Corp. – begins to face generics in 2022.

Opdivo continues to be overshadowed by Merck & Co. Inc.'s competing PD-1 inhibitor Keytruda (pembrolizumab), which dominates the first-line non-small cell lung cancer (NSCLC) market where Opdivo has yet to be approved – and which has reduced the number of patients in need of second-line treatment, where the Bristol drug is approved.

However, sales of the anticoagulant Eliquis (apixaban) continue to rise with room for additional growth, which will help boost overall revenue along with near-term launches from the company's Celgene-led late-stage pipeline.

Bristol reported $7.9bn in fourth quarter revenue and $26.1bn for the full year – up 42% and 22%, respectively, from 2018 – which largely reflected the closing of the Celgene acquisition on 20 November and the recognition of more than a month's worth of sales for Revlimid and the other purchased products. Bristol recognized $1.3bn in revenue from the multiple myeloma blockbuster Revlimid during the last six weeks of 2019. The fourth quarter beat analyst consensus of $7.1bn even though Opdivo sales fell short of expectations with a 2% year-over-year decline to $1.76bn for the quarter; sales of $7.2bn for the year were up 7% from 2018. William Blair analysts had anticipated $1.83bn in fourth quarter Opdivo sales despite recent quarter-over-quarter declines (*see table on following page*).

NEW OPDIVO INDICATIONS COMING, INCLUDING 1L NSCLC

While Bristol did not provide any detailed Opdivo sales guidance, the company is sticking with its prior expectations that the product's sales are likely to decline in 2020, but grow again in 2021 following approvals by the US Food and Drug Administration and other regulators this year for additional indications, including first-

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line NSCLC. *(Also see "Bristol Projects Opdivo Sales Will Grow Again In 2021" - Scrip, 31 Oct, 2019.)*

"Opdivo grew on a full-year basis and though we are seeing some pressure in the US, as expected, we saw growth internationally and continue to view 2020 as a year of transition for the brand," CEO Giovanni Caforio told the earnings call. "Looking forward, we have the potential for new launches, supporting an expected return to growth in 2021. This includes first-line lung cancer with studies 227 and 9LA, our first-line original cancer opportunity with 9ER, and moving into earlier-stage disease with a number of adjuvant opportunities."

The US FDA is expected to make a decision by 15 May on use of Opdivo and Bristol's CTLA-4 inhibitor Yervoy (ipilimumab) for first-line NSCLC based on the CheckMate-227 study. *(Also see "Keeping Track: Nektar Withdraws Oxycodegol NDA As Novel Submission Pileup Continues" - Pink Sheet, 20 Jan, 2020.)*

While CheckMate-227 showed an overall survival benefit, Bristol said on 31 January that it pulled a marketing authorization application (MAA) filed with the European Medicines Agency (EMA) after the EMA's Committee for Medicinal Products for Human Use (CHMP) determined it could not make a decision on the MAA due to the multiple protocol changes to the study. *(Also see "BMS Ready To Pounce On Non-Chemo Opportunity In Lung Cancer With Checkmate-227 Data" - Scrip, 25 Jul, 2019.)*

However, the company does anticipate filings in the US and EU this year for Opdivo/Yervoy in first-line NSCLC in combination with two cycles of chemotherapy based on the survival outcome in CheckMate-9LA. *(Also see "An Early Surprise Win For BMS's Opdivo/Yervoy In Lung Cancer" - Scrip, 22 Oct, 2019.)* Filings also are planned based on the CheckMate-9ER study testing Opdivo plus the Exelixis Inc. kinase inhibitor Cabometyx (cabozantinib) versus Pfizer Inc.'s kinase inhibitor Sutent (sunitinib) in previously untreated advanced or metastatic renal cell carcinoma (RCC).

"Opdivo will likely slightly fall in 2020 due to shrinking market potential in lung cancer as patients continue to shift to Merck's Keytruda, which has strong data in the first-line setting," Morningstar analyst Damien Conover said in a 6 February report. "We expect Opdivo will gain a new indication in the first-line lung cancer setting in 2020-21, which should return the drug to growth in 2021. Additionally, we expect relatively stable sales of Opdivo in renal cancer and melanoma in the US, which drives over half of current US sales."

The analyst's comment is in line with commentary from Bristol's new chief financial officer David Elkins, who said during the earnings call that while the pool of second-line NSCLC patients is declining by about a third, the company expects steady Opdivo performance in melanoma and RCC to remain stable, with growth across indications internationally. Elkins noted that 20% of Opdivo's sales are in lung cancer with 26% in RCC, 29% in lung cancer and 25% in other tumor types.

Bristol's chief commercialization officer Chris Boerner added that the pressure on Opdivo sales in the US primarily comes from three second-line settings – NSCLC, small cell lung cancer, and head and neck cancer.

"And in those [latter] two tumors, it's a very similar dynamic to lung cancer, where you've seen competitive approvals in the first-line impacting eligibility in the second-line," Boerner added. "But I would say, importantly, our assumption for this year is that our

Bristol's Near-Term Launches

While Bristol's highly anticipated TYK2 inhibitor BMS-986165 is being studied in Phase III psoriasis clinical trials, all five of the company's near- and mid-term launches come from Celgene's pipeline:

- A US FDA approval decision is expected in March for the S1P receptor modulator ozanimod in multiple sclerosis.
- The FDA may decide on a second indication for erythroid maturation agent Reblozyl (luspatercept) in anemia associated with very low to intermediate risk myelodysplastic syndromes (MDS). It was approved for transfusion-dependent beta-thalassemia in November.
- FDA approval for the CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy lisocabtagene maraleucel (JCAR017, liso-cel) for adults with relapsed or refractory B-cell lymphoma is expected later this year after a BLA filing in December.
- A BLA filing is expected in the first half of 2020 for the B-cell maturation antigen (BCMA)-targeting CAR-T idecabtagene vicleucel (ide-cel, bb2121) in relapsed or refractory multiple myeloma, setting the stage for FDA approval later in the year or early in 2021.
- A submission to the FDA is being prepared for CC-486, an oral version of Celgene's hypomethylating agent Vidaza (azacitidine), as maintenance therapy after chemotherapy for acute myeloid leukemia (AML) patients who are ineligible for hematopoietic stem cell transplants.

Bristol's Quarterly Opdivo Sales In 2019

US sales declined in each consecutive quarter and dropped year-over-year during the last two quarters. Global sales fell consecutively in Q3 and Q4, but year-over-year only in the fourth quarter.

	2019 GLOBAL	2018 GLOBAL	CHANGE	2019 US	2018 US	CHANGE
Q1	$1.801bn	$1.511bn	19%	$1.124bn	$938m	20%
Q2	$1.823bn	$1.627bn	12%	$1.112bn	$1.024bn	9%
Q3	$1.817bn	$1.793bn	1%	$1.088bn	$1.141bn	-5%
Q4	$1.763bn	$1.804bn	-2%	$1.020bn	$1.136bn	-10%

Source: Bristol-Myers Squibb Co. earnings reports

shares in the second-line setting across those tumors remain stable. It's just stable within a smaller pool of patients."

OTHER NEAR- AND LONG-TERM GROWTH DRIVERS

Analyst questions about Opdivo's prospects dominated Bristol's earnings call despite the fact that it's not the company's biggest growth driver currently. Eliquis delivered $2bn in fourth quarter sales, up 19% year-over-year, while the novel oral anticoagulant (NOAC) generated $7.9bn in 2019 sales, up 23% from full year 2018.

"In the fourth quarter, we saw continued strong sales growth of 19% globally due to increased demand in both [atrial fibrillation] and [venous thromboembolism]," Elkins said. "Eliquis continues to increase its share at the expense of warfarin in an expanding NOAC class. As the class has expanded, we've seen Eliquis taking share at the expense of other NOACs."

"We continue to view this brand, which remains the number-one NOAC globally, as one positioned for significant future growth and continued opportunity for patients," he added. That growth plus the addition of Celgene's commercial portfolio and R&D pipeline, with four potential near-term launches, will contribute to growth that Bristol anticipates in 2020 and 2021. The company's guidance for this year anticipated total revenue of $40.5bn to $42.5bn in 2020 with non-GAAP earnings per share (EPS) coming in at $6 to $6.20 versus analyst consensus of $42.2bn in revenue and $6.21 in non-GAAP EPS this year. Bristol also provided 2021 non-GAAP EPS guidance of $7.15 to $7.41 versus consensus of $7.41, but didn't offer a revenue forecast for next year.

"While near-term growth looks solid, generic pressures will intensify in early 2022 with the staggered generic entry of Revlimid (close to 25% of 2020 expected sales), but new pipeline drugs should help mitigate pressures. We expect Teva and Alvogen to begin a partial generic Revlimid launch in early 2022, increasing to a full launch by 2026, based on [patent litigation] settlements," Morningstar's Conover wrote.

He said new drug launches should help offset the impact of Revlimid generics (*see box on opposite page*).

"As we look beyond 2020, we see a robust growth in 2021 driven by the current portfolio as well as new expected launch opportunities and the impact of continued synergies, all of which is reflected in the EPS guidance," Elkins said. "We expect continued growth into 2022 while acknowledging this will be a moderated growth rate due to the generic competition for Revlimid."

Bristol anticipated $2.5bn in "synergies," or cost reductions, for the combined Bristol-Celgene organizations, with one-third of that realized in 2020.

"As I said in the past, we continue to expect significant cash flow from the newly combined businesses and we will continue to employ a balanced approach to capital allocation. Business development is a key enabler of our strategy and therefore remains the top capital priority," Elkins said.

He noted that paying dividends to shareholders and buying back stock from investors also is a priority. Bristol announced that it will conduct another $5bn in share buybacks on top of the $1bn in stock that it still plans to repurchase from shareholders under a prior buyback program.

Published online 6 February 2020

BMS/Celgene Post-Merger Early R&D Strategy: Partnerships Are Still Key, Vessey Says:
https://bit.ly/2unvBoJ

Coronavirus Notebook: China Focuses On Antivirals As Death Toll Passes SARS

BRIAN YANG brian.yang@informa.com

As every day brings a surging fatality count, China's fight against the novel coronavirus outbreak is becoming a race against time.

The latest official data from the country's National Health Commission (NHC) show that the current situation has become far worse than with SARS (severe acute respiratory syndrome) in 2003.

As of midnight on 9 February, there were 35,982 confirmed cases (of which 6,484 were classed as severe) and that day alone 97 new deaths, bringing the official total to 908. What's alarming is that the death toll outside the epicenter of Hubei Province is increasing, with two deaths in Anhui and one each in Jiangxi, Heilongjiang, Hainan and Gansu provinces. The total number of recorded fatalities has now surpassed the 744 in the SARS outbreak.

As the figures rise, all eyes are turning to potential antivirals. In an interview with *Scrip*, the CEO and founder of Shanghai-based Ark Biosciences Inc., Jim Wu, said the outbreak would likely provide a growth opportunity for such products in the country, especially for smaller developers. ArkBio is already developing a treatment for respiratory syncytial virus, ziresovir.

Source: Brian Yang

People slowly return to work with protection on Beijing subway

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Best Practices In Seasonal Vaccine Efficacy Studies: Tips For Successful Planning And Execution

Classical, randomized placebo-controlled efficacy studies of vaccines for seasonal illnesses, such as influenza and respiratory syncytial virus (RSV), must conform to the calendar and run like clockwork. Typically, they are very large studies – with tens of thousands of subjects – and operate within a compressed timeframe dictated by the respiratory season. Thus, they cannot be undertaken as "business-as-usual," but rather require accelerated processes, rapid decision-making, and a different approach to risk. Here, we outline the challenges in these studies and share our recommendations for study planning, enrollment, surveillance and study closeout. With the right planning and support, these challenging studies can be completed successfully within the narrow seasonal window. Similar content is presented in our downloadable webinar ***(ICONplc.com/webinar-vaccinestudies)***.

SEASONAL STUDIES: A Wild, Rollercoaster Ride For Clinical Operations

While no two seasonal vaccine efficacy studies are truly alike, they all aim to prevent laboratory-confirmed disease. They also share several challenges that make for an intense and busy time for sponsors, contract research organizations and sites:

- **An aggressive calendar.** There is a narrow window of time during which study execution can occur. Ensuring vaccine availability, site activation and the recruitment and vaccination of thousands of subjects in a compressed timeline can therefore be challenging. There is no "wiggle room" in the schedule, so not starting early enough and unexpected setbacks can put a study at risk for a delay. Depending on the study plan, this could mean a 6-12 month delay; six months if a two-hemisphere study had been planned and 12 months with a planned single hemisphere study.

- **Rapid, competitive recruitment of thousands of subjects.** Most seasonal virus studies enroll 7,000 to 10,000 subjects, and it is not unheard of to have 14,000 or more. All sites must be ready to go simultaneously, and all subjects must be enrolled in a short period of time (usually about eight weeks) and before they would otherwise be vaccinated in the case of influenza. Often, by the time the vaccine is manufactured and released, there is little time to spare. Enrollment must commence immediately and be completed within approximately two months, with hundreds to thousands of subjects enrolling every week. The sheer volume can be challenging.

- **Active surveillance throughout the respiratory season.** It is critical that the study captures all respiratory symptoms and that subjects be swabbed for virus identification. Subjects need to be proactively contacted and reminded to report protocol defining respiratory symptoms. The number of symptoms required may vary from study to study, so the site must be very aware of the protocol defining symptoms for the study that is conducting. Recently we have seen protocols only requiring one symptom of a certain duration, whereas prior studies typically required two symptoms – generally one respiratory and one systemic.

THINK AHEAD: The larger the study or the shorter timeline = the faster the pace = more work in a compressed time period

Start early and adhere to timelines

- Rapid decision-making
- Frequent escalations and quick resolutions
- Internal advocates to prioritize seasonal studies

Not business as usual

- Accelerate site ID, phone PSVs, regulatory/submissions process, SIVs at risk
- All sites (within a hemisphere) start competitive enrollment on or about same day

All systems live at time of FSI

- EDC, eDiary, eTMF, CTMs, etc.
- 12-16 wks. plus buffer

Continuous management of eTMF

- High volume of data/documents
- Ensure inspection ready at all times

Close oversight of disease surveillance and sample collection

- Capture all disease
- Ensure plan to capture subjects that cannot come to site for NP swab

- **Complex supply logistics.** It can be difficult to have sufficient volume of the study vaccine (and/or the comparator vaccine) and ancillary study supplies (rulers, thermometers, diaries, swabs, blood collection supplies, etc.) on hand for study start and without interruption during study conduct. Vaccines must be distributed via a cold chain, and provisions need to be in place to quickly replace any product that might be affected by a temperature excursion so as to not cause recruitment delays. Ancillary supplies typically require a larger storage area, which many sites may not have. Thus, plans also need to be in place to ensure sufficient supplies are on site at all times to preclude recruitment pauses.

- **High volumes of data and documents.** The sheer number of subjects and the use of patient-reported outcomes (PROs) for reactogenicity – either with paper diaries or eDiaries – produce large volumes of data that must be entered and cleaned. Sites must be prepared to enter in real time and the data management team must perform in-stream data cleaning, as any backlog magnifies quickly.

The Basics Of Study Design

Relative to influenza, in most developed countries like the US, there is a recommendation that everyone be immunized for influenza. This creates an ethical dilemma and can put high-risk subjects (infants and elderly) at risk in a placebo-controlled study. In studies of young, healthy adults, a placebo can be used since the population is generally at low risk for experiencing serious consequences from contracting influenza. However, this requires that subjects be fully informed of the recommendation that they receive a vaccine as the standard of care. They must understand that participation in the study means they may be randomized to a placebo and that their alternative to study participation is to receive the influenza vaccine. In the high-risk populations (such as in infants, young children, elderly and those with chronic disease) the study must include an active comparator vaccine for influenza. For RSV, there is currently no approved vaccine, so a placebo-controlled study is currently not an issue.

Relative to influenza, in most developed countries like the US, there is a recommendation that everyone be immunized for influenza.

Seasonal vaccine studies can be based anywhere in the world as influenza and RSV are ubiquitous. However, sponsors tend to prefer conducting them in the Northern Hemisphere where the research and regulatory environment is more developed and predictable, surveillance is good and there is a season with a somewhat predictable robust peak. Closer to

the equator, the RSV and influenza season tends to occur year-round with smaller peaks in the rainy season and in the winter. Several APAC countries have good infrastructure and very good recruitment, and thus can serve as additional countries if enrollment needs to be extended. Many sponsors opt to initiate their studies in North America and then to expand to APAC and/or the Southern Hemisphere, to have greater exposure and to mitigate for any unanticipated delays that may compromise the enrollment period. ICON has been very successful with the North America only or North America plus APAC models in studies ranging from 4,600 to over 14,000 subjects.

Once the protocol is stabilized, the hemisphere and countries where the trial will run should be selected. These decisions will affect the selection of the Contract Research Organization (CRO), labeling, shipping, importation and distribution requirements and timelines.

Planning

Not only is the timeline for seasonal vaccine studies extraordinarily compressed, but there are also potentially serious consequences for any delay. If the trial cannot be started within the optimal window, it will typically have to wait a full year for the timing to be appropriate once again unless a mitigation to bring on the opposite hemisphere is already in motion. The trial plan must, therefore, be comprehensive and also address possible contingencies. In order to help ensure the smooth conduct of the trial, sponsors should engage their research partners at least nine to 12 months in advance of study start for the Northern Hemisphere (NA and EU) and slightly longer for Latin America, China and Japan. US-only studies with all private sites have the shortest timeline and generally, seven to nine months is adequate.

The first critical step is to stabilize the protocol; it is difficult to prepare an extensive study plan if the protocol is still in flux. This should be completed nine to 12 months prior to the expected date of the First Subject In (FSI). The inclusion/exclusion criteria for the study should be considered carefully, recognizing that they can unnecessarily limit enrollment. Consider, for example, the impact of excluding subjects who received a flu vaccine in the last 12 months vs. the last six months, or the need to set restrictive blood pressures or body mass indices. Not only can these decisions restrict enrollment, they may affect labeling downstream. In general, the criteria should be as unrestricted as possible while ensuring that the subjects are generally healthy, or health stable in the case of the elderly or high-risk special populations, so that the data are not confounded by issues related to chronic disease.

Once the protocol is stabilized, the hemisphere and countries where the trial will run should be selected. These decisions will affect the selection of the Contract Research Organization (CRO), labeling, shipping, importation and distribution requirements and timelines.

The monitoring plan should then be developed, along with any monitoring oversight plan. The monitoring frequency and the sponsor's involvement in monitoring oversight will affect the budget, so these factors should be settled early and communicated to the research partner.

The investigator budget will need to be developed early and will need to account for staff time, study procedures, a stipend for participants and the monitoring parameters established in the monitoring plan. Given the number of subjects typically involved, the investigator budget will be substantial, and it will be important to get it right before contract negotiations with sites begin to avoid delays.

The leading reason that studies fail to meet their FSI dates and or face enrollment challenges is a delay in supplying sites with the test vaccine and/or the comparator vaccine. The manufacturing plan should have time built in, if possible, for batch failures. If it becomes clear that supplies will be delayed, the CRO should be notified at once so that sites can be notified and can manage their plans as well.

It is also important to make sure that the selected sites have all of the necessary equipment to handle vaccines and lab specimens, which include centrifuges and refrigerators/freezers. This is rarely an issue in the Northern Hemisphere, but might be a consideration in Latin America and APAC where space or equipment may need to be rented for the study duration

System development is also a critical part of the startup process. Generally, it can take six to 12 weeks to set up and test study systems such as eDiaries electronic data capture (EDC), interactive response technology (IRT), electronic trial master files (eTMF) so that they are live prior to first subject randomized.

All such systems need to be stress tested so that all sites can be activated at the same time. Similarly, all support systems, such as the help desk, need to be fully prepared for the volume of activity that will be required upon study start.

And of course the statistical analysis plan (SAP) and any plans for an interim data analysis should be set prior to the FSI.

Manage The Volume

Enrollment

All sites within a hemisphere should begin competitive enrollment on or around the same day. To avoid over-enrollment, sponsors should know in advance how they will cap enrollment either at the site or the country level. Generally, with competitive enrollment, a country level cap is preferred to ensure that enrollment goals are met and that one or two slower enrolling sites do not compromise the completion of on-time enrollments.

Preferably, screen failures should be captured in the IRT or EDC. Should the screen fail rate be higher than anticipated, data will be available in real time to assess the situation so that mitigations can be put in place quickly, as appropriate.

These studies are well suited to risk-based monitoring as a way to both reduce costs and help study teams focus on what really matters: subject safety and the integrity of endpoint data.

Sites will be processing multiple subjects daily, and need to spend sufficient time with subjects on their first visit to make sure that they understand the study requirements, risks and benefits, and how to complete the diary. It is critical that sites review the diary requirements for collecting reactogenicity data with subjects as well as the surveillance process if diary alerts are part of the surveillance plan. Most sponsors opt for eDiaries due to the volume of subjects and the other advantages of digital data collection: real-time safety oversight, documentation of when the diary was completed and the fact that traditional, on-site monitoring of the data by a CRA is not required. Paper diaries have many shortcomings, including the workload to monitor and reconcile thousands of subjects and the resulting challenge to ensure the highest data quality.

Adverse Event Reporting

All vaccine studies collect reactogenicity data, solicited local and systemic symptoms, via an electronic or paper diary. In years past and in most studies today, it has been assumed that any local reaction is definitely related to the vaccine and that systemic symptoms were possibly related, due to temporal association. Recently we have seen a couple of sponsors request that the investigator rate the causality of each symptom recorded. This has created a large work burden for the site and is something that requires careful thought and consideration if it is necessary. We've had two clients tell us it was requested by the FDA; however, we see that most clients do not require this assessment.

General, adverse events (AEs) or medically attended adverse events are generally captured for 28 days post vaccination, while serious adverse events (SAEs) are reported for the duration of the trial.

Data Monitoring And Study Documentation

These studies are well suited to risk-based monitoring as a way to both reduce costs and help study teams focus on what really matters: subject safety and the integrity of endpoint data. Options include targeted or randomized monitoring, reduced source document verification, and/or data analytics. Selection of the best solution is in large part driven by the risk tolerance of the client.

The eTMF, of course, is the documentation of the study and must be overseen closely with active, real-time filing and periodic quality checks throughout the duration of the study. Again, due to volume, failure to keep the filing up to date and reviewed for quality can prolong the study close and compromise the study integrity.

Stay On Top Of The Data

Because these studies move so quickly, data will be coming in very rapidly, and it is essential to clean it continuously, rather than letting it wait until just before the study closes. The same is true for serology, viral swabs and the reconciliation of SAEs.

Ideally, the final database lock is completed in two stages; safety lock followed by laboratory lock. It is usually possible to lock the safety database 21 days after the last subject visit, although this can be challenging because it is possible to have 10,000 or more subjects completing their last visit within one week. It typically takes three to four weeks, or more, for the final serology/virology results to come in, and thus, that portion of the database will be locked several weeks after receipt of the final laboratory data. Another approach taken by some sponsors is to lock

the safety database and then handle the serology analysis outside of the safety database.

Closeout site visits should be conducted within four to eight weeks of the safety database lock to ensure study integrity and inspection readiness, as sites quickly move on to other studies and institutional memory starts deteriorating. Because the laboratory data may not yet be available at the time of closeout, sites must be advised of that fact and that they may receive additional queries around the lab data. Generally, once the lab data are in and reconciled, sites will be advised to notify their international review board (IRB) of study closure.

Success Factors

Seasonal vaccine studies are fast-paced from beginning to end. In our experience, the keys to success include:

- Careful early planning, strong communications and close collaboration between the sponsor, the CRO, the sites and other vendors.
- Making the study a priority within the organization with internal advocates.
- Selecting sites that are experienced in vaccine studies and have proven their capabilities.
- Taking extraordinary steps to ensure the availability of the study vaccine and any comparator.
- Aggressively addressing any unanticipated delays.
- Using a robust system for tracking progress and gathering data.
- The ability to make decisions and resolve issues rapidly (ideally within 48 hours).
- Considering out-of-the-box solutions to ensure on-time site activations.

Seasonal vaccine studies present challenges for even the most experienced and prepared study managers. The scope and timeframes of these studies leave no room for error and have a steep learning curve with limited leeway to learn on the job. They call for a comprehensive, coordinated approach that accounts for contingencies, properly manages risk, holds to a firm schedule and applies best practices developed through years of experience.

Cynthia Dukes, PA-C, MT

***Vice President*, Drug Development Services, Vaccines, Infectious Disease**

Cindy Dukes is a therapeutic expert for vaccines and leads ICON's Vaccine Centre of Excellence. She has over 40 years of diversified clinical experience, including infectious disease and vaccines. In a global survey by Vaccine Nation, Cindy was recognized as one of the "Top 50 Influential People in Vaccine Development" in 2014. In 2016, she received a Distinguished Alumnus Award from Baylor College of Medicine for her leadership in vaccine development. *PharmaVoice* recognized Cindy as one of the "Top 100 Leaders in the Industry" in 2016. Under her leadership, ICON received the "Best CRO" award at the Vaccine Industry Excellence Awards in 2014 and 2017.

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"For small biotech companies like us, we will initiate drug discovery efforts in the [coronavirus] area, not for the sake of making money but to provide a weapon to safeguard the society and mankind," Wu said in an interview.

RACE TO A CURE

The Chinese government sees the lack of antiviral treatments for the fast-growing and single largest health threat to the country as an urgent issue. In a surprise visit to the Institute of Pathogen Biology under the Chinese Academy of Medical Science, Chinese Premier Li Keqiang said on 9 February that such drugs are needed to ease the public's fear and panic about the outbreak.

So far, two antivirals are under clinical study against the coronavirus in China, Gilead Sciences Inc.'s repurposed Ebola drug remdesivir and AbbVie Inc.'s Kaletra (lopinavir and ritonavir). Meanwhile, researchers at the institute have already screened 3,000 potential drugs, of which around 30 are under further testing.

Antivirals aside, the global biopharma sector is also moving ahead with work on vaccines, including Nasdaq-listed Inovio Pharmaceuticals Inc., which has received $9m in funding from the Coalition for Epidemic Preparedness Innovations (CEPI). The US biotech has teamed up with Beijing's Advaccine to make the potential vaccine, INO-4800, available for clinical study in China "as soon as possible", Inovio CEO Joseph Kim told *Scrip*.

The local partner in China will facilitate the regulatory filing and oversee the local Phase I clinical study, which is currently planned to start sometime in the early summer, Kim added.

The timing, however, may not be as fast as some people are hoping for and scaling up manufacturing is another major challenge. The CEPI funding will be used towards scale-up preparations for Inovio's vaccine but will only last through the summer, so the company may need additional money to get full production up and running.

ArkBio's Wu shares similar concerns. "My projection is before any drug is developed [except for drugs already under clinical development], the virus will be long gone," he told *Scrip*.

Coronavirus Coverage

Coronavirus Notebook: Gilead Readies Remdesivir, China Expedites Clinical Approvals: https://bit.ly/2SgrWSs

Coronavirus Notebook: Remdesivir Enters Study, Outspoken Physician's Death Sparks Anger: https://bit.ly/2UHOJZ8

Coronavirus Notebook: Regeneron, HHS To Develop Antibody: https://bit.ly/31Ev65R

Coronavirus Notebook: China Generic Antiviral Filed For Emergency Approval: https://bit.ly/2uqPlb4

GSK Joins Race To Tackle Coronavirus: https://bit.ly/38f5sqT

"My projection is before any drug is developed except for drugs, already under clinical development, the virus will be long gone."– Jim Wu

URGENT NEED

For now, the need to get effective antivirals and vaccines to the front lines in Wuhan hospitals remains acute. As the confirmed cases in the city surpass 10,000 and some patients can't even get a hospital bed, local physicians have been scrambling to cope with a chronic shortage of medical supplies, protective clothes and available medical staff.

Other companies in the global biopharma sector are expediting work on antivirals and vaccines against 2019-nCoV, which China's NHC has now renamed Novel Coronavirus Pneumonia (NCP). US firms Moderna Inc., Johnson & Johnson and Regeneron Pharmaceuticals Inc. and GlaxoSmithKline PLC in the UK are all now involved in the effort.

In South Korea, Abclon Inc. is working to co-develop a therapeutic antibody for 2019-nCoV with the Korea Research Institute Of Chemical Technology. Under the agreement, the two firms will assess antibodies that can neutralize new and mutated coronavirus and can precisely diagnose antigen proteins. Abclon will handle production while the institute will verify therapeutic effects using cell and animal models.

Abclon said it has technology and know-how in discovering antibodies that are efficient and effective against specific antigens. Using its platform technologies such as novel epitope screening and optimized antigen technology, the firm is progressing antibodies and CAR-Ts in cancer and autoimmune diseases.

A few other South Korean companies and research institutes such as ImmuneMed and the National Institute of Health are also known to be developing new coronavirus vaccines and other therapies, but few details are available so far.

In general, the development process could last longer than the outbreak, predicted ArkBio's Wu. "I do believe vaccine development is very important to prevent future coronavirus outbreaks. I foresee many companies, including big or smaller firms, will keep working in the area."

(With contributions from Jung Won Shin in South Korea.)

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Novartis's Inclisiran Unscathed As Arrowhead Falls Short

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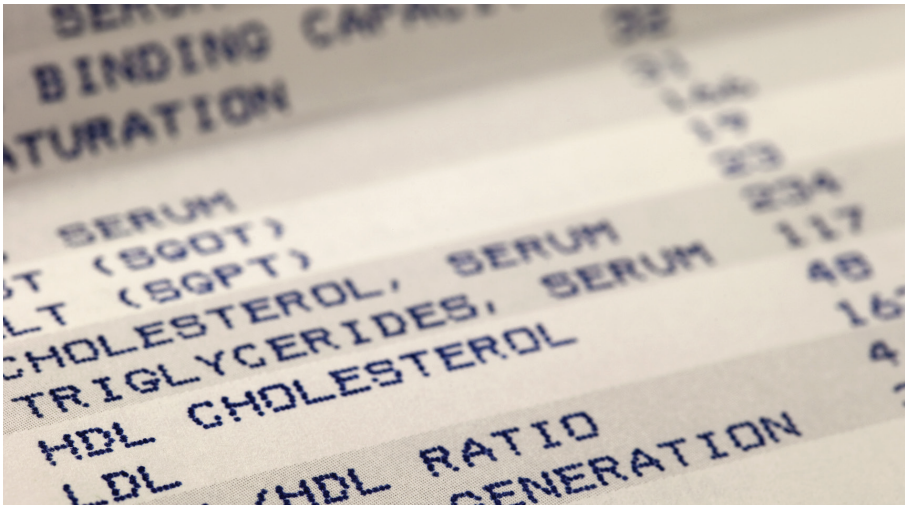
Novartis AG remains in pole position with its RNA interference (RNAi) therapy inclisiran after results from rival Arrowhead Pharmaceuticals Inc. fell short of challenging its results in lipid-lowering.



The Swiss big pharma company jumped into the field last year when it acquired The Medicines Co. for $9.7bn on the promise of its late-stage RNAi drug inclisiran (developed by RNAi trailblazer Alnylam Pharmaceuticals Inc.).

It produced compelling Phase III data from its latest ORION-10 trial in November, significantly lowering "bad" LDL cholesterol in patients with atherosclerosis. The trial showed a placebo-adjusted reduction of 56%, adding to similar results from earlier trials, which were filed with the FDA in December.

Following on behind is another RNAi platform company, Pasadena, CA-based Arrowhead. It had two RNAi-based cardiovascular therapy candidates reading out interim Phase I/IIa results this week – but its LDL-targeting drug fell short of inclisiran's performance.

Interim data showed ARO-ANG3 produced a mean maximum reductions in LDL-C of 39-42% after a period of at least 29 days.

Analysts at SVB Leerink pointed out that the Arrowhead's trial design saw its data presented as mean maximal reduction at 30+ days, compared to a time-averaged value from days 90-540 of follow-up in the Novartis study, one of several factors which helped flatter Arrowhead's results.

ARO-ANG3 is injected once every four months – a dosing regimen which the company believes could be extended to six months, which it would need to achieve to match the schedule Novartis is investigating with inclisiran.

The real test of these RNAi medicines will be cardiovascular outcomes trials (CVOTs), with inclisiran's already underway, though it won't read out until 2024.

Given that it is lagging far behind Novartis in developing its drug, and has now failed to match efficacy on lipid-lowering, analysts at SVB Leerink doubt whether ARO-ANG3 is worth taking into pivotal trials.

However all is not lost for Arrowhead, as it has a number of other candidates with potential in the RNAi field which is increasingly attractive to investors.

The company has also just presented interim Phase I/IIa results for ARO-APOC3. This targets apolipoprotein C-III (APOC3), and is a potential treatment for severe hypertriglyceridemia.

It is in pursuit of Ionis Pharmaceuticals Inc.' more advanced candidate AKCEA-ANGPTL3-LRx, which is being studied in patients with hypertriglyceridemia who also have type II diabetes and non-alcoholic fatty liver disease (NAFLD), and for which it recently acquired Pfizer as its development and commercial partner.

Interim data unveiled on 5 February showed that Arrowhead's ARO-APOC3 produced a mean maximum reduction in APOC3 of 97%, and a mean maximum reduction of triglycerides (TG) of 95% and a mean absolute reduction of TG of -3183 mg/dl.

Ionis is yet to release comparable data from its study, but ARO-APOC3's massive 95% reduction in triglycerides may well give it the edge. It already has a clear advantage in dosing, as it is administered once every four months, compared to the monthly dosing required for Ionis's candidate.

During a call with analysts, Arrowhead's CEO Christopher Anzalone also revealed interest from big pharma companies about its NASH candidate, HSD17B13, which is about to enter Phase I trials.

Big pharma is still on the look out for candidates with compelling safety and efficacy profiles against the condition, and Arrowhead says HSD17B13's novel mechanism makes it currently one of the most sought after assets in NASH. Dosing will begin shortly, and the company says it could have initial data by the end of 2020.

Arrowhead's lead candidate is ARO-AAT, a drug for alpha-1 liver disease. It has just entered an open-label Phase II study AROAAT2002, alongside SEQUOIA, an adaptive design, potentially pivotal Phase II/III trial, due to complete in 2023.

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Pfizer's Vyndaqel Success Interfering With Alnylam's Plans

ANDREW MCCONAGHIE andrew.mcconaghie@informa.com

Alnylam Pharmaceuticals Inc. is banking on its drug Onpattro becoming the foundation stone for a multi-billion dollar franchise in amyloidosis – but the runaway success of Pfizer's rival Vyndaqel could upset those plans.

Onpattro (patisiran) became the first-ever RNA interference (RNAi) therapy to reach the market in August 2018, licensed to treat polyneuropathy in patients with the rare life-limiting condition hATTR amyloidosis. Nevertheless, it got off to a slow start in first few months on the market, held back in part by the difficulty in diagnosing patients and gaining reimbursement for its high price ($450,000 for a year's treatment in the US).

Alnylam has just unveiled its Q4 and full year results, however, which show Onpattro sales gaining momentum, rising to $55.8m in the final quarter, with Japan and European markets adding to US revenues.

Central to the company's strategy is to gain approval for Onpattro and its follow-on drug vutrisiran to treat cardiomyopathy in the closely related but distinct (and much more common) conditions of hereditary and wild-type ATTR amyloidosis.

Patisiran is currently in late-stage trials for the condition, but Pfizer Inc. has leapt into the lead in ATTR-cardiomyopathy.

Speaking on a Q4 results call with analysts, Alnylam CEO John Maraganore spelled out his great empire-building ambition for the company:

"We believe that our approach in silencing the production of ATTR with RNAi therapeutic has a potential to be the best-in-class mechanism in ATTR amyloidosis. We also believe that the potential opportunity for patisiran and then vutrisiran in the ATTR amyloidosis cardiomyopathy indication … could represent a multi-billion-dollar anchor opportunity for building Alnylam, similar to what Regeneron had with Eylea, or Celgene with Revlimid."

However, standing between Alnylam and that kind of blockbuster success is Pfizer, which launched Vynaqel (tafamidis) in the US in June for ATTR cardiomyopathy with an annual list price of $225,000.

John Maraganore, CEO of Alnylam

Pfizer's Angela Hwang

Vynaqel has exceeded all sales expectations, hitting $79m in Q3, its first full quarter on the market, way ahead of consensus forecasts of 21m.

It maintained that as the year closed, achieving a remarkable $213m in the final quarter of 2019.

A more convenient formulation, Vyndamax, was launched in September (one daily pill instead of four) which will only help boost the drug's rapid rise to $1bn annual sales this year.

Central to Alnylam's plan to catching up with and overtake Pfizer are trials to prove the value of Onpattro and its follow-up vitusiran in cardiomyopathy in both hereditary and wild-type ATTR amyloidosis patients.

The first study is Apollo B, a Phase III trial of Onpattro. This involves around 300 patients, with its primary endpoint being a six-minute walk test with important secondaries including the rates of death and hospitalizations.

The study is expected to complete enrolment towards the end of 2020, and if the results are positive, Alnylam will file in a late 2021 to early 2022 timeframe.

Also already underway are two Phase III studies of its next-generation candidate, vutrisiran, which is delivered by a quarterly subcutaneous injection. The first is HELIOS-A, which is enrolling hereditary ATTR amyloidosis patients with polyneuropathy, with top-line results expected in early 2021, with HELIOS-B in cardiomyopathy expected in the second half of that year.

The problem for Alnylam is this time lag gives Pfizer lots of opportunity to capture the cardiomyopathy market – and it is already putting its considerable resources behind raising the diagnosis rate among this hard to identify population.

All the same, Pfizer's head of BioPharmaceuticals Angela Hwang said at its recent Q4 call that it was "still a very dynamic situation because we're really relatively new in this process," warning that she expected to see some quarter-to-quarter fluctuations in sales.

One key development to watch for this year is whether or not Pfizer can make Alnylam even more uncomfortable by gaining a license in polyneuropathy, which would see it encroach on its rival's niche. Angela Hwang told analysts that Pfizer was only exploring the possibility with the US Food and Drug Administration, but could gain this approval rapidly, given it already has this license outside the US.

Alnylam, meanwhile, can look to the rollout of Givlaari, *(Also see "Alnylam Wins FDA Approval For Givlaari, Its Second RNAi Drug " - Scrip, 20 Nov, 2019.)* the expected approval of its third product lumasiran and royalties from Novartis-owned inclisiran later this year to help increase its growth – but will have to wait somewhat longer before it has a blockbuster of its own.

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Leo Sets Up For A David & Goliath Showdown In Atopic Dermatitis

JESSICA MERRILL jessica.merrill@informa.com

Danish dermatology specialist Leo Pharma AS thinks it can leverage tralokinumab to become a global leader in atopic dermatitis, a big ambition given the competition in the space. The interleukin-13 blocker is a pillar of the company's expansion outside of topical psoriasis treatments, where it has a strong position.

The company is poised to file tralokinumab with the US Food and Drug Administration and the European Medicines Agency in 2020, though it has not given a specific timeline. The small dermatology company will be going up against two big biopharma rivals, Regeneron Pharmaceuticals Inc. and Sanofi, which market the blockbuster atopic dermatitis treatment Dupixent (dupilumab), and other big pharmas are coming behind.

"We are very excited about this opportunity and the potential for us to bring to the market in the atopic dermatitis space the second available treatment," CEO Catherine Mazzacco said in an interview. *Scrip* talked to Mazzacco about the potential launch and Leo's growth strategy at the J.P. Morgan Healthcare conference on 14 January.

A YEARS LONG GROWTH STRATEGY TAKES SHAPE

Mazzacco joined Leo in August from outside the company to lead the expansion into medical dermatology. She has experience launching immunology biologics, having worked at Abbott Laboratories Inc. during the launch of Humira (adalimumab), before it was spun out into the company that is now AbbVie Inc.. She was most recently head of global commercial operations for GE Healthcare's biopharma division. The timing of the leadership transition, with Gitte Aabo stepping down, comes as Leo, in 2018, initiated a new 2025 business strategy, with the goal of launching several new drugs during the timeline.

"It's a very exciting moment to join Leo," Mazzacco said. "We are clearly signaling that we are transforming our company to expand from a heritage of experience in dermatology to more of this traditional pharma portfolio, towards finding and bringing in innovation."

The company gained rights to tralokinumab in skin diseases from AstraZeneca PLC in 2016 for a reasonable upfront of $115m. The deal includes up to $1bn in commercial milestones, however, and mid-teen tiered royalties on product sales. Eli Lilly & Co., meanwhile, just agreed to pay $1.1bn in cash to acquire Dermira Inc. to gain a rival IL-13 blocker, lebrikizumab, in Phase III.

AstraZeneca offloaded tralokinumab for dermatology as part of a strategy to focus on its core therapeutic areas: respiratory, oncology and cardiometabolic disease. The company had been developing tralokinumab for asthma, but it failed in Phase III trials.

Leo also gained European commercial rights to the IL-17 inhibitor brodalumab from AstraZeneca at the same time. Leo markets brodalumab as Kyntheum in Europe, and in 2019, the company gained rights to the drug in select other ex-US countries from Bausch Health Companies Inc., which holds the US rights to the drug. Brodalumab's commercial uptake has been limited versus some other IL-17 inhibitors because of a safety warning on suicidal thinking.

Tralokinumab, if approved by the FDA, would have a healthy head start in the market over lebrikizumab, but it would launch into what is expected to be a competitive market for atopic dermatitis drugs that is currently led by Dupixent. Several other new drugs are advancing through late-stage development for atopic dermatitis, including oral JAK inhibitors.

Dupixent, meanwhile, is getting enhanced attention under Sanofi's new CEO Paul Hudson, who set an ambitious €10bn revenue target for the drug as part of his turnaround plan for the company. *(Also see "Sanofi's €10bn Dupixent Plan: 'We're Going To Put The JAKs Properly In Their Place'" - Scrip, 12 Dec, 2019.)*

A DIFFERENT PRODUCT PROFILE

Tralokinumab and dupilumab work differently, however, and while Regeneron and Sanofi have already secured approval of Dupixent in three indications and have plans for its development to treat many more allergic diseases, Leo is focused solely on skin diseases. Dupixent blocks IL-4 and IL-13, while tralokinumab only blocks IL-13.

Sanofi and Regeneron believe IL-4/IL-13 are the master regulator for Type 2 inflammatory disease, which encompasses many diseases. Leo believes IL-13 is the key cytokine associated with atopic dermatitis and that the specificity will provide an advantage when it comes to treating a skin disease that effects a heterogeneous population, exec VP-R&D Kim Kjoeller said.

"What is the most important is the quality of the product that we will be providing to the market," Mazzacco said. "When we discuss with the key opinion leaders who have been involved in our several clinical trials, there is the same feedback from all of them – that there is a need for this treatment in the treatment paradigm."

Leo presented top-line data from three Phase III trials testing tralokinumab in December. Two of the studies, ECZTRA 1 and ECZTRA 2 were randomized, double-blind, placebo-controlled trials that evaluated tralokinumab as monotherapy in adults with moderate-to-severe atopic dermatitis. ECZTRA 3 measured the safety and efficacy of tralokinumab in combination with topical corticosteroids. The company said all three studies met their primary endpoint: Investigator Global Assessment (IGA) score of clear or almost clear skin at week 16 and at least a 75% or greater change from baseline in their Eczema Area and Severity Index (EASI) score at week 16. The company said it will present the full data in 2020.

Mazzacco said Leo has been building out a commercial team in the US to support the launch of tralokinumab. "We have been investing significantly these past years and it was in preparation of this upcoming potential launch," she said. "We

have been building the last two years progressively a team in the US with the right competencies and the right skills that we believe will be able to provide this product successfully to the marketplace."

A UNIQUE BUSINESS MODEL

Leo Pharma doesn't answer to public or private investors. The company is funded by the Leo Foundation, which was established in Denmark in 1984, with the aim of supporting skin disease research and establishing Denmark as a global leader for dermatology research. The Leo Foundation owns financial assets of around DKK-18bn ($2.66bn), provides financial support to Leo Pharma and funds philanthropic grants, according to the foundation's 2018 annual report. The Leo Foundation is the sole shareholder of Leo Pharma. Leo Pharma generated DKK10.4bn ($1.54bn) in 2018, roughly flat with 2017 revenues. Operating profit was DKK1.61bn ($237m), a substantial increase from DKK852m ($126m) in 2017 driven by the divestment of Leo Pharma's non-strategic dermatology portfolio to Karo Pharma AB, resulting in a net gain.

Leo may be small, but Mazzacco said the company is one industry should pay attention to because behind tralokinumab, the company is developing other systemic drugs for dermatology indications, with a focus mainly on atopic dermatitis but a desire to expand to rare diseases.

"Our vision is super clear and simple: We want to build upon our legacy and reputation in dermatology to really find and bring innovative treatments to a larger number of patients in dermatology," she said. The company has a strong commercial presence in topical treatments for mild-to-moderate psoriasis but is making a substantial push into atopic dermatitis.

Leo's pipeline of drugs for atopic dermatitis includes: delgocitinib, a pan-JAK inhibitor in development as a topical treatment; AGRX-112, an anti-inflammatory monoclonal antibody; and an H4R antagonist as a potential oral treatment.

"Then, there is clearly a willingness to go beyond eczema and psoriasis, and we have been making a clear first step in rare diseases," she said. In November 2018, Leo signed a partnership with PelePharm Inc. to develop patedegib, a topical gel for the prevention of Gorlin syndrome, a severe rare skin disease for which there are no approved therapies, committing $70m up front. The deal included back-end milestones and an option to buy the company outright.

Published online 6 February 2020

Stockwatch: Gilead, BMS Expose High Cost Of M&A

ANDY SMITH

Expensive acquisitions are in the spotlight during earnings season. The purchases of Kite and Celgene by Gilead and Bristol-Myers Squibb are not turning out to be what was written on the tin.

As earnings season trundled into its third week, Gilead Sciences Inc. needed its full-year 2019 financial report to dispel any worries that its $11.9bn acquisition of Kite Pharma Inc., which spearheaded its move into CAR-T therapy, was an over-optimistic gamble.

The portents from Novartis AG's recent full-year 2019 financial report, which showed its CAR-T product Kymriah (tisagenlecleucel) generated $278m in sales in 2019, up from $76m in 2018, were not good. Although analysts' consensus estimates for Kymriah had been $237m, expectations had already been lowered. There is a growing presumption that the CAR-T acquisitions of Kite by Gilead and of Juno Therapeutics Inc. by Celgene Corp. will not yield a blockbuster any time soon.

GILEAD: MORE MISSES THAN HITS

Gilead's fourth-quarter 2019 revenues of $5.9bn beat analysts' estimates of $5.7bn and were just above the $5.8bn booked in the fourth quarter of 2018. Its non-GAAP earnings per share (EPS) of $1.30, however, missed the consensus estimates of $1.67. The full-year 2020 guidance for non-GAAP EPS was $6.05-6.45, which also missed the analysts' estimate of $7.01.

Gilead's CAR-T product Yescarta (axicabtagene ciloleucel) had a better launch than Novartis's Kymriah, and that continued in the fourth quarter of 2019 with Yescarta recording sales of $122m against Kymriah's $96m. However, another announcement would dull the shine of Yescarta's halo.

Quarter-on-quarter revenue growth of $4m for a product that only launched at the end of 2017 paled into significance when compared with the announcement of another $800m impairment charge related to the Kite acquisition. Gilead probably hoped that the 8% increase in dividend for the first quarter of 2020 would redress the earnings dilution resulting from the write-down and would have the same supportive effect on its stock price that a similar announcement did for Roche the previous week. Those hopes were in vain. Gilead's stock price dropped 2.8% on the day after the after-market announcement and this held the share price back to finish the week up 2.5% against the NASDAQ Biotech Index's 3.4% weekly rise.

DO SOMETHING, BUT ONLY SOMETHING GOOD

Gilead has been caught between a rock and a hard place for many years. Since acquiring Pharmasset Inc. for $11bn and doubling its revenues with a leading HCV franchise that complemented its HIV franchise, investors have been asking (perhaps unfairly) "What's next?" The subsequent combination of aggressive competition in HCV and the slowing of growth in its HIV franchise has stunted Gilead's growth. At virtually every earnings call, analysts ask Gilead's management what the company will buy after Pharmasset, to which management intones from a well-rehearsed script about valuations and the consideration of many possibilities.

Gilead has found that spending $11bn to double its sales is a very rare event and a more likely transaction involves spending $12bn only to write it down by significantly more than the revenues generated in successive years. Gilead's shareholders are now probably split between those wanting it to spend big on another Pharmasset and those who breathe a sigh of relief at the end of each quarter that it has not spent big on another Kite. Gilead probably

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

PIPELINE WATCH, 31 JANUARY–6 FEBRUARY 2020

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Top-Line Results	AbbVie Inc.	Rinvoq (upadacitinib)	Psoriatic Arthritis	SELECT-PsA1; Met Primary Endpoint	9	70
Phase III Top-Line Results	Zogenix, Inc.	Fintepla (fenfluramine oral)	Lennox-Gastaut Syndrome	Adjunctive Therapy; Positive Results	6	58
Phase III Top-Line Results	Bio-Thera Solutions Ltd.	BAT-1706 (bevacizumab biosimilar)	Non-Small Cell Lung Cancer	vs. Avastin; Met Primary Endpoint	0	35
Phase II/III Top-Line Results	United Therapeutics Corp.	Unituxin (dinutuximab)	Small Cell Lung Cancer	DISTINCT; Mixed Results	-10	25
Phase III Trial Initiation	Eisai Co., Ltd.	Lenvima (lenvatinib)	Head and Neck Cancer	LEAP-010; First-Line Use	-	35
Phase III Trial Initiation	Adial Pharmaceuticals, Inc.	AD04 (low-dose ondansetron)	Alcohol Use Disorder	ONWARD; Initially In Finland	39	51
Phase II/III Trial Initiation	Sanofi/Regeneron	Dupixent (dupilumab)	Bullous Pemphigoid	LIBERTY-BP; Double-Blind Study	59	59

Source = Biomedtracker; LOA = Biomedtracker's opinion on likelihood of approval.

CONTINUED FROM PAGE 21

hoped that both groups would have been pacified by a hike in the dividend. However, the stock price performance from last week suggests that Gilead still has more of the former investors, who aspire to sales and earnings growth.

BMS'S EXPENSIVE BOLT-ON OF CELGENE'S REVENUES

At first glance, the 2.9% stock price rise of Bristol-Myers Squibb Co. (BMS) in the week of its fourth-quarter 2019 earnings announcement (compared to the NYSE ARCA Pharmaceutical Index's 1.0% rise for the week) told a different story of its acquisition of Celgene than Gilead's did of Kite. BMS reported fourth-quarter 2019 revenues of $7.9bn, which were comfortably ahead of consensus estimates of $7.1bn. Non-GAAP EPS of $1.22 also substantively beat analysts' estimates of $0.88, while full-year 2020 non-GAAP EPS guidance of $6.00-6.20 bracketed analysts' estimates of $6.12. There was apparently nothing not to like in the announcement as the BMS share price rocked up 3% in the pre-market trading on the day of its announcement and maintained that rise for a week.

At the same time as BMS was reporting its fourth-quarter 2019 financial results, a group of my Cambridge University Masters students were presenting their analysis of BMS plus Celgene. This was because having chosen to analyze BMS, the transaction only closed in the last quarter of 2019, so they effectively had to assess and value two companies for the mark of one. Their conclusion was that both companies were undervalued by the market (which is undeniable) and that the cost savings would help carry the deal. One of their arguments was that when BMS first reported as a combined company, the market would appreciate the value of the Celgene's bolted-on revenues. The analysis is logical and the optimism admired, but two points bear mentioning.

BMS's stock price prior to the transaction had been depressed because its anti-PD1 monoclonal antibody Opdivo (nivolumab) had long since surrendered its lead in the anti-PD1 space to Merck & Co. Inc.'s Keytruda (pembrolizumab). Indeed, Merck's fourth-quarter results earlier in the week rubbed salt into this wound with Keytruda's fourth-quarter revenue growing to $3.1bn (against Opdivo falling quarter-on-quarter to $1.7bn), while Merck also beat consensus estimates of revenues and EPS.

Celgene's stock price prior to the announcement of its acquisition by BMS had also been declining because of the impending loss of exclusivity of its biggest product Revlimid (lenalidomide). BMS paid $74bn for a wasting asset which bolted on a one-time $1.9bn quarterly revenue gain and resulted in a 3% stock price rise. I'm sure my students were expecting more stock market appreciation. Is it any wonder that most pharma M&A fails and the only people who benefit are the fee-earning bankers?

Andy Smith gives an analyst and former investor's view on life science companies. He joined the research house Equity Development in October 2019 having previously been an analyst at Edison group and a Senior Principal in ICON PLC's Commercialization, Pricing and Market Access consulting practice. Andy has been the lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, was awarded the techMark Technology Fund Manager of the year for 2007 and was a global product manager at SmithKline Beecham Pharmaceuticals.

Published online 10 February 2020

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Laurence De Moerlooze	Bavarian Nordic AS	Chief Medical Officer and Executive Vice President	Takeda Vaccines	Vice President, Global Lead, Zika and Norovirus Vaccines	1-Apr-20
Craig T. Basson	Boston Pharmaceuticals	Chief Medical Officer	Novartis Institutes for Biomedical Research	Global Head, Translational Medicine, Cardiovascular and Metabolism	3-Feb-20
Laurence Reid	Decibel Therapeutics	Chief Executive Officer	Warp Drive Bio	Chief Executive Officer	29-Jan-20
Sara Bonstein	Insmed Incorp	Chief Financial Officer	OncoSec Medical Inc	Chief Financial Officer and Chief Operating Officer	31-Jan-20
Vesa Kataja	Kaiku Health	Chief Medical Officer	Central Finland Health Care District	Chief Medical Director	1-Feb-20
David Zaccardelli	Verona Pharma plc	Chief Executive Officer, President and Director	Dova Pharmaceuticals Inc	Chief Executive Officer and President	1-Feb-20

Click here for all appointments: https://bit.ly/2oHWRYn

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