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A Muted J.P. Morgan, But The Focus Is Execution – And That's Good News

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The atmosphere at the J.P. Morgan Healthcare Conference was muted this year, without any big deal news, or any substantial news at all. At first the quiet opening on 13 January was unsettling, but over the course of the meeting the undercurrent shifted to a sense that the pharmaceutical industry is on solid footing as it moves into a new decade, executing on focused business strategies.

The dust has settled on 2019, when several sizable mergers were announced or closed – Bristol-Myers Squibb Co. and Celgene Corp., AbbVie Inc. and Allergan PLC, Takeda Pharmaceutical Co. Ltd. and Shire PLC, Mylan NV and Pfizer Inc.'s Upjohn, and Roche and Spark Therapeutics Inc., for example. Investors were hoping J.P. Morgan would start the year off with a similar buzz as last year, when Eli Lilly & Co. announced the $8bn acquisition of Loxo Oncology Inc.. *(Also see "J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room " - Scrip, 9 Jan, 2019.)* But the value of assets is high and many big biopharma companies are well positioned for moderate near-term organic growth, so the urgency for deals is tempered.

That doesn't mean deals won't happen in 2020. Many of the industry's top biopharma leaders said they expect to keep a similar pace of business development activity in 2020. For a few like Gilead Sciences Inc., with money to spend, the onus is on them to get a deal done.

POISED FOR EXECUTION

Novartis is in the process of launching multiple new drugs. Pfizer, this year, will have cycled through its last big patent loss for a six-year time horizon and is pivoting to be a smaller innovative pharma company. GlaxoSmithKline PLC is beginning to see the first fruits of its R&D revamp approaching the market under the leadership of Emma Walmsley and Hal Barron.

AstraZeneca PLC has big new growth drivers to focus on in oncology, including Enhertu (trastuzumab deruxtecan) and Calquence (acalabrutinib) and just filed roxadustat for anemia in chronic kidney disease. Merck & Co. Inc. is confident in the continued growth of its mega-blockbuster Keytruda (pembrolizumab), which is annualizing $1bn per month in revenues.

Merck CEO Kenneth Frazier characterized Keytruda as being in the early middle innings of the game during a fireside chat at J.P. Morgan. "It may be the beginning of the fourth inning, but remember every inning is different and a lot more runs get scored in some innings than others, and we think there are a lot of runs left to be scored."

In an interview, Novartis's new pharmaceuticals president Marie France Tschudin summed up the sentiment across many big pharma companies this year. "It is a fantastic time to be at Novartis and really in pharma," she said. "We have a really clear strategy around where it is that we want to go, which is fueled obviously by our pipeline."

Takeda president of R&D Andrew Plump reflected that it had been the first calm J.P. Morgan for the company since he joined the Japanese pharma in 2015. "This was the first time we haven't had a big event to announce and it was just so nice, to be now a company that's starting to create a stable foundation," he said. "We are build-

CONTINUED ON PAGE 4

Gilead's Future
Daniel O'Day says firm will still dominate HIV (p14)

J&J's Power Launches
J.P. Morgan meeting hears 10 are due in four years (p11)

J.P. Morgan Meeting
Bourla says Pfizer 'underappreciated', GSK's myeloma first (p5-7)

from the editor

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PwC has just published its annual global CEO survey, showing a remarkable turnaround in business leaders' expectations regarding economic growth. While only 5% of those surveyed expected declining economic growth in 2018, the proportion has risen to 53% in 2020. Meanwhile, the proportion who were "very confident" about their own organization's prospects for revenue growth fell to 27% in 2020 from 42% in 2018.

The pharma industry is balanced in a global environment in which there are broad anxieties about geopolitical stability, trade conflicts and climate change, while the fourth industrial revolution, driven by artificial intelligence, has the potential both to disrupt and displace businesses as well as to bring tremendous opportunities for progress.

Four *Scrip* reporters were in San Francisco last week for the J.P. Morgan Healthcare conference, and their coverage of the various strategic updates made during the meeting suggests that pharma is a sector more focused on the opportunity than the threat, overall.

As Jessica Merrill noted in the cover story, this year's conference was not one of those mercurial M&A-fueled jamborees that roil biopharma stocks. Rather the mood was of dedication to the task of making good on the many promises that technological and biomedical advances have brought to industry's pipeline. Industry leadership has been through a period of high turnover, and science and R&D are regaining primacy as the driving force for growth. Big pharma executives talked about their openness to bolt-on acquisitions and their focus on delivering meaningful and innovative therapeutic advances in a limited number of focus areas. And they expect science to translate into profits.

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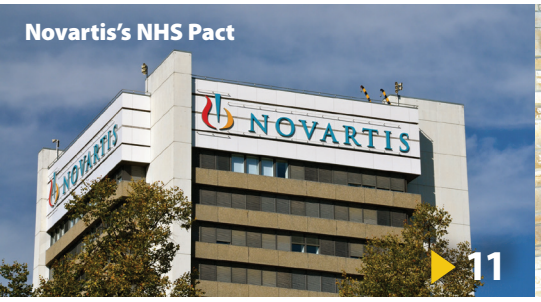

exclusive online content

Companies Deepen Therapeutic Focus: The EY Firepower Report

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Portfolio optimization in a small range of therapy areas, the continuing need to access innovation, and a focus on specific business models, are expected to drive M&A and deal-making activity in 2020, says the *2020 EY M&A Firepower report*, launched at the start of this week at the J.P. Morgan meeting in San Francisco.

"Portfolio optimization could generate nearly $300bn in deals in just five therapy areas," the report claims. A majority of companies have acute growth gaps driving near-term need for deals, and around a half of biopharma companies still need to increase their therapeutic focus, the report adds.

"In 2019, almost every major biopharma acquisition increased both the buyer's overall therapeutic focus and its projected five-year compound annual growth rate," the EY report notes. 20 of 25 deals analyzed by EY involved a high degree of overlap between the purchaser's existing portfolio and the therapy area or indication of the lead product of the target company.

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

inside:

CONTINUED FROM PAGE 1

ing on what we put together over the past few years and it's really great."

Across the industry, Plump said, there has been a similar feeling going into 2020. "There's huge progress across companies in terms of focus, in terms of reducing waste, in terms of trying to drive spend in a responsible way, in terms of adopting new technologies."

A lot of industry's focus is stemming from advancement in science in areas like immuno-oncology, gene editing and gene therapy that present an opportunity to make an impact on serious diseases. But unlike some years at J.P. Morgan, where the thrill of a scientific breakthrough is still new and palpable, this year the industry is digesting the first commercial experience with new advances, for example in genetically defined cancer with drugs like Roche's Rozlytrek (entrectinib), in RNAi with Alnylam Pharmaceuticals Inc.'s Onpattro (patisiran) and Givlaari (givosiran) and in gene therapy with Novartis's Zolgensma.

DEALS WILL FOLLOW

Industry leaders said they are still eager to supplement their pipelines through business development. Genentech's chief medical officer and head of global product development Levi Garraway said in an interview that he expects Roche to continue executing on business development at a similar pace.

He joined the company from Eli Lilly last year. "One of the things I've admired about Roche and Genentech from the outside is the consistent activity," he said. "The great thing about innovation is that no matter where you are, there is always far more innovation outside your doors than inside your doors."

Takeda's Plump said the company has earmarked a similar amount of money toward business development as it did in 2019, both of which is higher than the 2018 spending commitment.

Pfizer CEO Albert Bourla, from center stage of the Grand Ballroom at the Westin St. Francis, reaffirmed his business development strategy. "We want to acquire or in-license programs Phase II-ready, Phase III-ready, these programs that can become medicines in 2024, 2025, 2026, 2027," he said. Other biopharma CEOs like Gilead's Daniel O'Day, Bristol's Giovanni Caforio and Biogen Inc.'s Michel Vounatsos also reaffirmed their commitment to business development.

PwC's US pharmaceutical and life sciences deals leader Glenn Hunzinger said there are lots of deals brewing. "There is a ton of activity underneath the hood," he told *Scrip*. He predicted a similar amount of business development activity in 2020 as 2019, with $5bn to $15bn deals being the sweet spot.

"This conference has been a lot more calm than last year. Most people we speak to feel good about where they are, they have good assets, their pipeline is good," he added.

THE BIG UNCERTAINTY – US DRUG PRICING

Drug pricing reform in the US and mounting political pressure remains the big uncertainty, particularly in an important election year. Industry would like to see drug price reforms that reduce the cost burden on patients and out-of-pocket costs but are lobbying against policy changes that would change the way Medicare negotiates drug prices or would rely on international drug prices as benchmarks.

Across the industry, leaders acknowledge that if patients can't afford their medicines no one is succeeding.

Regeneron Pharmaceuticals Inc. CEO Leonard Schleifer, asked about the political environment in a breakout session, said "We hope that market-based solutions would be the way that the problem could be solved. It is clear, this is the United States of America. People should be able to have access to drugs. They shouldn't go bankrupt. They shouldn't have to choose between food and their insulin or not be able to take a drug that can prevent blindness. That's just unacceptable."

Despite the frustration, industry is still pushing rebate reform talking points even though the prospect for policy change on that front seems as dead as inhaled insulin – at least in the near term. The US Congressional Budget Office forecast HHS's rebate reform proposal would increase federal spending on Medicare Part D by $170bn from 2020-2029, which ended enthusiasm for being the political party responsible for implementing the kind of change that could increase costs. *(Also see "Pharma's Big Defeat: US Rebate Proposal Hits The End Of The Road" - Scrip, 11 Jul, 2019.)*

Nonetheless, industry leaders including the chief lobbyist, the Pharmaceutical Manufacturers and Researchers of America (PhRMA) CEO Steve Ubl, Bristol's Caforio, who is PhRMA chairman, and Roche Pharmaceuticals' CEO Bill Anderson, used a drug pricing panel at the conference to continue advocating for rebate reform.

"We think rebate reform is a no-brainer," Anderson said during the panel. Caforio added, "The real issue is that the rebates are not used to lower the exposure of patients to the cost of care. The rebates are used primarily to reduce the monthly cost of healthy individuals."

While pricing transparency would be welcomed by many, widescale rebate reform doesn't appear to be on the near-term horizon. What is approaching, however, is the 2020 US election, which could bring a new US president and changes in the Republican-controlled Senate, which is currently viewed by industry as a welcome barrier against a House bill, HR3, that would allow the federal government to negotiate drug prices in Medicare. *(Also see "US Government Drug Pricing 'Negotiation:' Where We Go From Here" - Scrip, 13 Dec, 2019.)*

"We are a little bit agnostic who sits in the White House," AstraZeneca Biopharmaceuticals exec VP Ruud Dobber said in an interview. "Our main objective is to make sure patients can afford their medicines and there is access, whether it is President Trump or Democratic candidates."

One policy Dobber and other industry leaders said they support is a Senate proposal that would cap out of pocket costs for seniors, which has some bipartisan support. *(Also see "Senate Drug Pricing Bill Lowers Manufacturer Discounts In Part D Catastrophic Phase" - Pink Sheet, 6 Dec, 2019.)*

"We clearly believe out-of-pocket costs are too high so a cap on the out-of-pocket costs is critical moving forward and at that point, it is irrespective of whether you are Republican or a Democrat," Dobber said.

No big policies are expected to get significant attention in an election year, but the drug pricing debate will continue and the outcome of the election could set a very different tone for J.P. Morgan in 2021.

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J.P. Morgan Notebook: Bourla Feels Pfizer's Underappreciated, GSK Prepares For Myeloma First

MANDY JACKSON ANDREW MCCONAGHIE JESSICA MERRILL

ALBERT BOURLA ON WHAT THE STREET HAS WRONG ABOUT PFIZER

Pfizer Inc. CEO Albert Bourla is one year into the job and tried to impress upon J.P. Morgan Healthcare Conference attendees at a fireside chat in the Grand Ballroom at San Francisco's Westin St. Francis how much the company's innovative R&D business has changed. Pfizer is set to update investors on 2019 financials and 2020 forecasts on 28 January, but Bourla said there is a lot of upside in the company's longer-range pipeline that Wall Street analyst forecasts aren't taking into account.

For example, in vaccines he said that while there are some forecasts for Pfizer's 20-valent pneumococcal vaccine, analysts aren't accounting for a *Clostridium difficile* vaccine in Phase III that will read out later in 2020, a meningococcal vaccine in Phase II, and a maternal vaccine for respiratory syncytial virus (RSV) in Phase II.

"In rare diseases, I know the Street projects the growth of tafamidis and now they increased Vyndaqel projections, but I haven't seen anyone having numbers for our gene therapy," Bourla said. Pfizer surprised investors with the success of its early launch of the Vyndamax/Vyndaqel (tafamidis) franchise last year for wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM).

Bourla said that Pfizer is poised to be a leader in gene therapy, but rarely gets the credit for that on Wall Street. The company has three gene therapies in clinical development, two more it gained through business development with Vivet Therapeutics and Therachon AG and another seven in preclinical development, he said. Pfizer paid $340m in May for Therachon, gaining a Phase I gene therapy for short-limbed dwarfism. *(Also see "Pfizer Grows In Rare Disease With $810m Dwarfism Company Buy" - Scrip, 9 May, 2019.)* Also in 2019, the company gained an option to buy Vivet, which was advancing a treatment for Wilson disease toward the clinic at the time. *(Also see "Pfizer Buys Option For Vivet In Latest Gene Therapy Tie-Up" - Scrip, 20 Mar, 2019.)*

"We are building in Sanford here in the US, the largest gene therapy manufacturing capacity in the world, and there's nothing, I think, in the projection of the Street about that," Bourla said. Pfizer announced last year a $500m investment in the construction of a gene therapy manufacturing facility in Sanford, NC.

In Pfizer's immuno-inflammation franchise, he said the company has five different JAK inhibitors in development across 10 different indications. "Only one of them I have seen some minor projections in the Street analysts," he said. "I can go on and on. What I want to say is that there is a significant gap."

Some of the responsibility falls to Pfizer, he said, which hasn't shone a big enough spotlight on the innovation going on. He announced the company will have its first R&D day in many years on 31 March. He also told investors that they can expect Pfizer to spend more on R&D going forward as a percentage of sales because the company plans to continue the same level of R&D investment even after it spins out the Upjohn business into a merger with Mylan NV.

The result is that Pfizer will go from being one of the lowest R&D spenders as a percentage of sales to one of the highest. Pfizer spent 14.8% of revenues on R&D in 2018.

Pfizer is poised to be a leader in gene therapy, but rarely gets the credit for that on Wall Street.

FIRST-IN-CLASS LAUNCH WILL TEST GSK'S CANCER CREDENTIALS

GlaxoSmithKline PLC is gearing up for the anticipated approval and launch of belantamab mafodotin, a first-in-class treatment for multiple myeloma that represents an important next stage in GSK's reinvention, since it is one of six anticipated new drug or line extension approvals in 2020.

Presenting at the J.P. Morgan conference, CEO Emma Walmsley recapped GSK's progress in transforming its product portfolio and internal culture during the last few years, stressing that "we have much more to do."

Belantamab is especially important as it will be a test of the company's re-entry into oncology, which it effectively exited in 2014 under previous CEO Sir Andrew Witty.

GSK hasn't launched a new cancer treatment since the melanoma combination of Mekinist (trametinib) and Tafinlar (dabrafenib) seven years ago, and that means it is now busy with a recruitment drive to rebuild its commercial expertise in the field.

Belantamab is an antibody-drug conjugate and the first drug to be submitted to the US Food and Drug Administration that targets B-cell maturation antigen (BCMA) in patients with relapsing and refractory multiple myeloma.

The drug may reach the market before any of its competitors, but two chimeric antigen receptor T-cell (CAR-T) therapies – bluebird bio Inc. and Bristol-Myers Squibb Co.'s bb2121 and JNJ-4528 from Johnson & Johnson and Legend Biotech Corp. – are not far behind. Bristol anticipates filing its CAR-T candidate for FDA approval during the first half of 2020. *(Also see "Bristol's CAR-T Strategy Comes Into Focus With Two Near-Term Filings" - Scrip, 10 Dec, 2019.)*

GSK's head of R&D Hal Barron has singled out belantamab for rapid development, and told investors at J.P. Morgan that its registrational DREAMM2 study produced "quite impressive" data. This remark skirts round the fact that the overall response rate (ORR) in the trial stood at just 31% – down a long way from the 60% ORR seen in an earlier study and far below the 100% response rate reserved to date with JNJ-4528. There also are safety concerns regarding the eye condition keratopathy.

At the same time, GSK can point to belantamab's advantages over CAR-T therapies, including convenience, cost and toxicities.

GSK's commercial head Luke Miels also outlined the company's efforts to build a new oncology organisation by hiring experienced sales reps.

"What we've tried to do is, from a strategic level right down to an operational level in the key markets, hire people who really know this area," Miels said. "Of course, there's a few mergers and things which are also disruptive, which put people into the marketplace who may not have naturally been out there looking, and we've taken advantage of that. So, I feel very comfortable with the teams that we've built."

GSK's oncology portfolio includes ovarian cancer treatment Zejula (niraparib), purchased in the $5.1bn acquisition of Tesaro Inc. that closed last year, plus multiple internal and partnered candidates that are central to the company's growth for the next five to 10 years.

ASTRAZENECA ON LAUNCHING ENHERTU

The launch of AstraZeneca PLC's Enhertu (trastuzumab deruxtecan) for metastatic HER2-positive breast cancer is expected to be a blockbuster, and exec VP-Oncology Business Unit David Fredrickson talked to *Scrip* at the J.P. Morgan Healthcare conference about the launch.

The drug, partnered with Daiichi Sankyo Co. Ltd., received accelerated approval from the US Food and Drug Administration on 20 December based on Phase II data, including a notable progression-free survival benefit in patients who have run through other treatment options. The market is expected to be a competitive one, however, with Seattle Genetics Inc. poised to launch tucatinib, a medicine that works differently but has also shown strong efficacy, in 2020. *(Also see "Data For Two HER2-Positive Breast Cancer Drugs Impress, Including On Overall Survival" - Scrip, 11 Dec, 2019.)*

Getting to the market first could be an advantage for gaining traction, Fredrickson said, though he expects both Enhertu and tucatinib will become part of the treatment paradigm for advanced breast cancer patients. "New options are good for patients always," he said. But, he noted, "the way I see things playing out is we are launched and we are available today." Positive early experience with the medicine is what will carry the most weight going forward from a competitive standpoint, he said, as that is what will drive more uptake longer term.

AstraZeneca and Daiichi are also poised to take advantage of patients who are waiting for a new option. "We do see and expect there are going to be some bolus of patients that are out there that are being treated with chemotherapy today," Fredrickson said, though he said he doesn't expect any patients who are responding to treatment with existing therapy would switch.

Enhertu does appear to carry a premium price tag. Leerink analyst Andrew Berens said in a 23 December note that the price per patient is approximately $13,300 per month, which would be $159,600 annually. Analysts at Datamonitor Healthcare calculated the wholesale acquisition cost at approximately $172,295 per year for an 80kg patient, given that dosing is weight based.

AstraZeneca wouldn't confirm the WAC for Enhertu, however, a contrary move given the push more recently by big pharma to be more transparent on pricing. Fredrickson said the price is in line with the value it offers and on parity with other innovative drugs in breast cancer.

LILLY PANS FOR GOLD, FILTERING OUT THE SAND FROM EXTERNAL R&D GEMS

Scrip spoke with Eli Lilly & Co. senior vice president and chief scientific officer Daniel Skovronsky about various programs in the company's research and development pipeline, which Lilly continues to fill with both internally discovered assets and externally sourced programs. The company was the only big pharma to announce a significant M&A deal around the start of the J.P. Morgan Healthcare Conference when it said on 10 January it would buy Dermira Inc. for $1.1bn.

"It's a deal that's perfectly lined up with our strategy of bolt-on acquisitions where the science is good, the probability of success is high, addressing a major unmet medical need in one of our therapeutic areas," Skovronsky said. "By the time you get through all of those filters, there's not too many deals that look like that, so we were really excited about this opportunity and pleased to announce the deal."

Lilly also came to J.P. Morgan in January 2019 with another big deal – the $8bn acquisition of Loxo Oncology Inc., leading to the recent formation of a new oncology R&D unit helmed by Lilly executives who came to the company through the Loxo deal. *(Also see "Lilly Taps Loxo Execs To Bring Back That Biotech Feeling" - Scrip, 5 Dec, 2019.)*

"Probably I spend more than half of my time here at J.P. Morgan doing business development – meeting with companies and scouring for great opportunities," Skovronsky said. "They're hard to find; we have to look at a lot of things to find a Loxo or a Dermira. I wish that we had more. I would happily do deals like these more often, but our standards are high."

He said Lilly is looking for good science, which includes drug mechanisms of action that are understandable and will translate into a high probability of success in areas of significant unmet need within the company's therapeutic areas – oncology, immunology, diabetes and neuroscience.

"And then the final big screen is on value," Skovronsky continued. "We have to be able to acquire things at a price that while fair for the company being acquired still creates value for our shareholders. Usually that's about Lilly seeing something that others don't see or being willing to create some upside on the asset through our unique capabilities. Dermira checked all those boxes this year as Loxo did last year."

Asking prices for such assets, he noted, "are also high in all areas, but probably particularly in oncology, and at the same time competition is high. We are competing against our peers, and sometimes companies larger than us, to get the best assets and the best companies."

AMGEN LOOKS TO CAPITALIZE ON INVESTMENTS IN GENOMICS

Amgen Inc. CEO Bob Bradway said in his 14 January presentation at the J.P. Morgan Healthcare Conference that the company's three most important words this year are execution, execution and execution. Commercial execution is key as the company continues to feel the impact of biosimilar and generic competitors for some of its biggest blockbusters, but newer products still are struggling to make up for the revenue gap.

Execution also is important for the company's research and development pipeline, where Amgen hopes its investments in deCode genetics EHF and other genomics capabilities will pay off through more efficient R&D processes and faster successes.

"We consider that we are the industry-leading company when it comes to integrating human genetics into our discovery research, and we significantly expanded those efforts through collaborations completed in 2019," Bradway said. "In addition, we're very focused on using next-generation proteomics technologies to enable us to combine information with our genetics portfolio to characterize the pathways in biology that we think are relevant for disease."

Scrip spoke on the sidelines of J.P. Morgan with Amgen executive vice president of research and development David Reese about the three strategic imperatives that the company's R&D effort is focused on across Amgen's three therapeutic areas – cardiovascular disease, immunology and oncology – including the use of genomics to bring medicines to the market faster.

First, the company is working on improving its success rate, where genomics and proteomics efforts are being used to not only identify new drug targets, but also identify appropriate patients for clinical trials. Second is reducing the development cycle time of getting a drug from discovery to the market, which takes about 10-14 years now, and Amgen has shaved about three years off of that process. Third is taking into consideration earlier in development barriers that keep patients from getting access to new drugs.

"We need to be sure the drugs we're developing and the evidence packages will allow drugs to get to the people that need them," Reese said. "We're infusing that thinking in R&D, internally and in partnering. That doesn't mean the commercial group is determining what research is done. We want hand-in-glove thinking. We want to make sure patients get our drugs and that we generate a return that allows us to continue to invest in R&D."

KARYOPHARM CEO SAYS XPOVIO LAUNCH IS 'BETTER THAN EXPECTED'

Karyopharm Therapeutics Inc. gave an early look at sales to date for its multiple myeloma drug Xpovio (selinexor) on 13 January, a day before CEO Michael Kauffman presented at the J.P. Morgan Healthcare Conference, and the executive told *Scrip* the launch "has been going a bit better than expected."

The US Food and Drug Administration approved Xpovio, a selective inhibitor of nuclear export, on 3 July for relapsed or refractory multiple myeloma patients who have gone through at least four prior lines of therapy. Karyopharm said sales totaled $17m-$18m in the fourth quarter versus analyst consensus of $15m; sales for 2019, starting with Xpovio's launch on 9 July, totaled $30m-$31m for the fiscal year.

"To date, the payer community has been pretty receptive; they understand how sick these patients are," vice president Ian Karp said. "We haven't seen denials for this drug – it just hasn't been a hurdle."

More than 550 doctors have prescribed Xpovio and more than 1,400 prescriptions have been filled as of 31 December.

Next up for Karyopharm may be a second indication in relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least two prior multi-agent therapies and who are ineligible for stem cell transplantation, including chimeric antigen receptor T-cell (CAR-T) therapy; the company submitted an application to the US FDA in December for this indication and will file later this year for European approval, following submission in early 2020 for multiple myeloma.

Also, results from the Phase III BOSTON study testing Xpovio in combination with Velcade (bortezomib) in second-line multiple myeloma are expected in early 2020, and if positive it will be filed with the FDA in 2020. Karp noted that this indication will expand the patient population eligible for treatment from 6,000 to 32,000 patients in the US. Karyopharm expects results from the Phase III SEAL study in patients with advanced, unresectable, dedifferentiated liposarcoma – Xpovio's first solid tumor indication – in mid-2020 with an FDA filing expected this year. Completion of enrollment in the Phase III SIENDO study of Xpovio as maintenance therapy in endometrial cancer patients is expected this year.

THE LAST LAUGH ON BIOPHARMA M&A

Truth be told, biopharma is a pretty serious business and light-hearted moments have been in short supply at the J.P. Morgan conference this year.

Meeting this unmet need on the second day of the conference was Francesco De Rubertis, co-founder and partner at Medicxi. The venture capital firm has many of the great and good from biopharma advising its investment plans, and enticed some of these big names to its event at a hotel away from the conference, high up on San Francisco's Nob Hill.

De Rubertis was leading a discussion about "New Shapes of the Pharma Industry in the Next Decade" with three industry heavyweights: Giovanni Caforio, CEO of Bristol-Myers Squibb, newly enlarged by the $74bn acquisition of Celgene Corp.; Jennifer Taubert, EVP, worldwide chairman, pharmaceuticals at Johnson & Johnson, and Vas Narasimhan, CEO of Novartis AG, one of the sector's most prolific M&A practitioners.

The conversation about business and M&A strategy was proceeding as normal until De Rubertis deadpanned: "So can you please tell us the names of the companies you are going to acquire?"

This raised a big laugh from the audience, who like everyone else attending J.P. Morgan were wondering when the next big M&A deal was going to land, since the conference kicked off without any large deals being unveiled.

Narasimhan eventually asked the biotech venture capitalist: "I have a question for you, Francesco. So, do you feel like a lot of biotech valuation expectations have gotten really out of hand?"

Francesco allowed the laughter to subside before answering simply: "No, I don't think so!"

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J.P. Morgan Notebook: Novartis CEO Weighs In On AI, Sangamo's Next Steps And More

JOSEPH HAAS MANDY JACKSON JESSICA MERRILL ANDREW MCCONAGHIE

SANGAMO HOPES TO DEMONSTRATE RELIABILITY IN HEMOPHILIA A

Sangamo Therapeutics Inc. may be months away from demonstrating that its gene therapy for hemophilia A – SB-525, partnered with Pfizer Inc. – offers best-in-class sustainability of its therapeutic effect, which is crucial because competitor BioMarin Pharmaceutical Inc. is positioned to get to market first with a gene therapy for the disease.

The potential of showing "reliability" represents Sangamo's best chance to overcome BioMarin's expected first-to-market advantage, CEO Sandy Macrae said at the J.P. Morgan Healthcare Conference on 16 January. The exec has previously explained that an optimal gene therapy for hemophilia A – replacing regular treatment with Factor VIII – must be "safe, reliable and predictable."

In San Francisco, Macrae said Sangamo has shown that SB-525 is safe and predictable in updated results from its Alta trial, but demonstrating reliability will only come from longer-term data expected in the next three to six months. BioMarin's Phase III program for valoctocogene roxaparvovec (valrox) showed some patients' Factor VIII levels eventually dipped below 50%, the bar for a diagnosis of hemophilia. An FDA action date for valrox is expected in August, and the product also is under review by the European Medicines Agency.

"We're waiting to see that we're reliable because that's the debate that everyone's having," Macrae said on 16 January. "Everyone's seen the results of our friends at BioMarin and wonders about the reliability of that medicine."

If a gene therapy for hemophilia A does not permanently correct the patient's Factor VIII level, retreatment presents a challenge because first-generation candidates produce an immune response in the patient that results in neutralizing antibodies to a subsequent dose. BioMarin is working on a next-generation adeno-associated virus (AAV) vector version of valrox that could enable re-treatment.

Macrae added that the Alta study has shown a peak effect within six to 10 weeks and that patients in the highest-dose cohort have had no bleeding episodes. Sangamo has transferred the SB-525 program to Pfizer under their 2017 partnership, with the pharma enrolling a Phase III lead-in trial. Pfizer plans to launch a pivotal study of SB-525 later this year. SB-525 and Roche/Spark Therapeutics Inc.'s Phase III SPK-8011 are thought to be a year or more behind BioMarin in reaching market.

Sangamo now can realize $300m between the completion of the investigational new drug (IND) application transfer to Pfizer and the first commercial patient for SB-525, Macrae said, after which it can earn sales royalties ranging from the low teens up to 20%. "One can imagine this having a substantial effect on the finances of Sangamo and it really will pay for our research in years to come."

Macrae said Sangamo's vision is to move beyond gene therapy. "Eventually, we will become more and more a cell therapy company. And then, ultimately, we will do gene and genome editing. And this range of modalities that we have at our fingertips allows us a range of medicines," the CEO noted.

> "Digital data science technologies can fundamentally give you an edge in decision making in your operations."
> – Vas Narasimhan.

NOVARTIS LEAVES FINANCIAL FORECASTING TO AI

While artificial intelligence (AI) and machine learning still suffers an image problem in the biopharma sector because of excessive hype, it is nevertheless becoming a part of day-to-day business in the industry. It was a recurrent theme at J.P. Morgan this year, with leaders citing its use from drug discovery to clinical trials recruitment to sales force productivity.

Novartis AG CEO Vas Narasimhan has made his company an early adopter of AI and data science technology, and says he believes rapid uptake can give it an edge over competitors.

Speaking at a spin-off summit of CEOs and R&D leaders hosted by health care venture capital firm Medicxi on 14 January, Narasimhan said Novartis has tried to adopt the technology broadly across the company, and at scale and speed.

"Digital data science technologies can fundamentally give you an edge in decision making in your operations," said Narasimhan.

He said that so far the biggest impact has been leveraging the technologies in Novartis's core operations, with chief digital officer Bertrand Bodson appointed in 2017 to lead 12 digital lighthouse projects to embed the technology across the business.

"To give you a concrete example, in 2020 our entire financial forecasts were generated by data science and AI," Narasimhan


Novartis's Vas Narasimhan

said. "We have AI generated predictions of every single product in every market, as well as optimization algorithms on how to optimize our investment and spending."

He added that commercial and other teams naturally engage in conversations about future product expectations, but that taking the forecasting responsibility allows them to focus on other aspects of the business.

However, it is clear that AI is no panacea.

Speaking on a second panel at the event, alongside other big pharma R&D leaders, Bristol-Myers Squibb Co.'s new president of research and early development Rupert Vessey agreed that AI was now "pervasive" in many R&D functions.

He couldn't resist making a tongue-in-cheek but nonetheless serious warning note on Novartis's forecasting application, however. He repeated the well known "garbage in, garbage out" observation that analytics technology can't perform well if the original data fed into it are flawed.

"Actually I'm really worried about the prediction of market valuation that Vas brought up. Because every single market valuation I have ever seen was wrong…and if they're putting the same data into the AI, it is just going to be wrong all over again!"

TAKEDA'S APPETITE FOR PARTNERING IS BIG

Takeda Pharmaceutical Co. Ltd. R&D President Andrew Plump said the company would be actively partnering in 2020. "We won't do major acquisitions. We don't have the capital or the interest or the need, but the model that we put in place, the R&D partnership model will continue as long as I'm here," he said in an interview at J.P. Morgan.

Takeda closed the $62bn acquisition of Shire a year ago and has largely completed the integration. *(Also see "Takeda's Weber: 'Everything Relies On Our Ability To Deliver Innovative Medicines' " - Scrip, 7 Jan, 2019.)* The company highlighted the combined pipeline at an R&D Day in November, with a therapeutic focus in four areas: oncology, rare disease, gastroenterology and neuroscience. *(Also see "Takeda: 12 NMEs Poised To Launch In Five Years, And Deliver $10 Bn In Peak Sales" - Scrip, 19 Nov, 2019.)*

At J.P. Morgan, Plump said the company had earmarked the same level of spending for business development in 2020 as it did in 2019. While a lot of the company's recent activity has focused on oncology, he said the therapeutic area with the biggest gap right now was rare disease.

In January, Takeda signed a small deal with Silence Therapeutics PLC to use the company's gene-silencing platform to generate siRNA molecules against an undisclosed target. *(Also see "Silence Signs Takeda Deal And Sets Sights On US" - Scrip, 7 Jan, 2020.)* Another interesting deal last year linked the company with MD Anderson Cancer Center to develop cord blood-derived CAR-directed NK cell therapies. In December, Takeda signed a bigger deal with Turnstone Biologics Inc. in which it agreed to pay $120m in upfront cash, equity and near-term milestones to collaborate on the development of multiple products using its vaccinia virus platform in cancer.

"We will clearly still look in oncology, but we actually have a nice portfolio of opportunities there," Plump said. "My guess is that we will be a little bit more active in the rare space, maybe neuroscience as well."

SAGE EXPECTS TO SEE ZULRESSO GROWTH IN SECOND-HALF 2020

Sage Therapeutics Inc. prepared investors for a slow ramp-up in sales for its postpartum depression (PPD) drug Zulresso (brexanolone) after the product's launch in mid-2019, and that will continue through the first half of 2020, Sage chief business officer Mike Cloonan told *Scrip* in an interview at the J.P. Morgan Healthcare Conference. *(Also see "Sage's Zulresso Launch Is Off, But Not Running " - Scrip, 6 Aug, 2019.)*

The company continues to work with hospitals to help them get certified under the Risk Evaluation and Mitigation Strategy (REMS) for Zulresso, which requires continuous monitoring of patients admitted for the drug's 60-hour infusion due to the risk of sedation and sudden loss of consciousness. Once certified and a treatment protocol is established, hospitals must negotiate reimbursement for the cost of the drug and the associated care.

"We're making a lot of progress with the 140 sites that are REMS-certified; 11 were treating at the end of Q3, so there's that gap between 140 and 11, because they have to work through those steps," Cloonan said.

Sage is working with hospitals and health care providers to create a sense of urgency and to share best practices from sites that have completed the certification and reimbursement processes to make more treatment sites available.

"What we've said is modest [sales] growth over the first half of the year while we build this foundation and then we expect a significant increase in revenue in the second half of the year while we have more sites set up and as we have the access for moms," Cloonan said. Payers have recognized the efficacy and the need for Zulresso as well with favorable reimburse-

ment policies for 75% of covered lives in the US, including commercial health plans and Medicaid.

"The payers recognize the unmet need; they're willing to cover Zulresso and we'll continue to work through that 25% that hasn't been established yet," Cloonan said.

Everything that Sage has learned from the Zulresso launch will benefit its second drug, SAGE-217, which is seen as a much larger opportunity as it's an oral drug in development for both PPD and major depressive disorder (MDD). The drug has generated positive Phase III results in PPD and mixed results in MDD, but the company will meet with the US Food and Drug Administration in the first quarter to discuss a path forward for SAGE-217 in MDD. *(Also see "Sage Still Sees Approval Path After Depression Drug Fails In Phase III Trial" - Scrip, 5 Dec, 2019.)*

"The market that '217 is going to launch into in postpartum depression is going to be different than the one that Zulresso launched into because of Zulresso. It's going to pave the way in many ways for '217," Cloonan said.

FREQUENCY AIMS FOR CLEAR SIGNAL IN HEARING LOSS TRIAL

Frequency Therapeutics raised $84m in its initial public offering in October 2019 based on its lead candidate for hearing loss, and the company is hoping that a Phase IIa trial reading out at the end of 2020 will help establish the potential of its technology.

The firm is working on small molecule candidates that can reactivate progenitor cells – providing a potentially far simpler and lower-cost way of regenerating cells within the body compared to cell or gene therapy platforms.

Its lead candidate, FX-322, will initially target a US market of around 30 million patients with sensorineural hearing loss (SNHL), the most common form of hearing loss, but could move on to a much larger global market.

SNHL is the most common form of hearing loss and results from damage to the hair cells in the inner ear or problems with the nerve pathways that convert sound waves from the inner ear to the brain. FX-322 is designed to treat

> "Payers are willing to cover Zulresso."

the underlying cause of SNHL by regenerating these hair cells through activation of progenitor cells already present in the cochlea.

CEO Michael Lucchino told the J.P. Morgan audience that progenitor cells are "underutilized assets that Mother Nature put in your body but [until now] there has been no way to turn them back on."

FX-322 has shown benefit in a Phase I/II study already, with more data on the way later this year.

Frequency has a deal with Astellas on ex-US rights to the drug, involving an $80m upfront payment, further milestone payments and double-digit royalties.

The company is planning an IND for its next candidate in the second half of 2021, a drug aimed at bringing about remyelination of nerve cells in multiple sclerosis.

REVANCE READIES FOR DAXI LAUNCH WITH DERMAL FILLER DEAL

Revance Therapeutics Inc. has responded to concerns that it might have a tough time selling its neuromodulator daxi (daxibotulinumtoxinA or RT002) to dermatologists and plastic surgeons without being able to offer a bundle of medical aesthetics products with discount pricing for the individual offerings – a strategy that has helped Allergan PLC boost sales for its blockbuster aesthetic Botox (onabotulinumtoxinA) – by bringing in a dermal filler line.

Revance announced on 10 January that it entered into an agreement with Teoxane SA to sell its Resilient Hyaluronic Acid (RHA) line of dermal fillers in the US and *Scrip* spoke with Revance CEO Mark Foley during the J.P. Morgan Healthcare Conference – where he presented on 16 January – about the strategic importance of the deal for daxi.

The company submitted its biologic license application (BLA) to the US Food and Drug Administration for daxi in the treatment of moderate-to-severe frown lines in November and it anticipates approval in the fourth quarter of this year – and it is hoping for a label in late 2020 that allows for treatment as infrequently as every six months, versus Botox's quarterly injections. *(Also see "Another Botox Competitor: Revance Prepares Longer-Lasting RT002 For BLA Submission" - Scrip, 22 Feb, 2019.)*

"Other more recent product launches suggest that overall in medical aesthetics physicians are open to trying new things," Foley said. "Having said that, when we looked at what other products to add to the bag, a filler was the most logical."

Teoxane's dermal filler line is approved in Europe and the US; Revance is hiring its sales team in anticipation of a second-quarter launch in the US. In Europe, Teoxane has sold more than 10m syringes. The agreement is a 10-year exclusive US distribution deal with the ability for Revance to extend the agreement for two more years.

"When daxi comes out, we will be established with user relationships," Foley said. "We feel very fortunate on the timing. It significantly strengthens our position in the marketplace."

As for the company's other partnership – a deal with Mylan NV for the development and commercialization of a Botox biosimilar – the big generics maker needed more time to decide whether to opt in to that opportunity because of its pending merger with Pfizer's Upjohn business into a new company called Viatris GMBH. *(Also see "Mylan Gets Until April 2020 To Decide On Biosimilar Botox Collaboration With Revance" - Generics Bulletin, 4 Sep, 2019.)*

"They came to us and said that because of the Upjohn relationship [they] need more time. They gave us another $5m to extend the relationship," Foley said. He noted that if Mylan has to walk away from the Botox biosimilar agreement, Revance is confident that another deal can be negotiated with one of the other companies that previously was interested in such a partnership. *(Also see "Mylan Set To Develop Biosimilar Botox In Deal With Revance" - Scrip, 28 Feb, 2018.)*

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J.P. Morgan Day 3: Skyrizi Momentum Builds, What's Next For Amarin, Viatris Debuts And More: **https://bit.ly/2TFqOsR**

Novartis Inks World-First Pact With NHS England For Inclisiran

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Novartis AG has unveiled what it claims is a world-first pact with NHS England that could give at-risk patients speedy access to the Swiss giant's investigational gene silencing cholesterol lower inclisiran, acquired through its recent $9.7bn purchase of The Medicines Company.

Inclisiran, a first-in-class small-interfering RNA (siRNA) drug that inhibits synthesis of PCSK9 which is expected to be a key growth driver for Novartis, is expected to be filed in the coming weeks. The Basel-headquartered company is already preparing for launch and has inked what it refers to as "a pioneering collaboration that brings together three projects that aim to tackle – directly or indirectly – the healthcare challenge of cardiovascular disease, whilst also providing increased opportunities for UK life science sector development."

First up is a proposal, upon regulatory approval and National Institute for Health and Care Excellence (NICE) assessment, to provide inclisiran for secondary prevention to atherosclerotic cardiovascular disease patients "through a population-level agreement." Novartis said that providing inclisiran to this high-risk population "could make a significant contribution towards meeting the NHS long-term commitment to preventing 150,000 cardiovascular deaths over 10 years."

The second proposal would see Novartis and the NHS explore "a large-scale clinical trial" to evaluate the use of inclisiran to patients at very high risk of having their first cardiac event, ie, primary prevention. The third facet of the pact includes the creation of an industry and academic consortium to look at manufacturing synergies "that could improve the efficiency and scale at which the UK can manufacture oligonucleotide medicines such as inclisiran."

Novartis CEO Vas Narasimhan said the company had "a unique opportunity with inclisiran to open up a new chapter in the treatment of cardiovascular disease, the world's leading cause of mortality and disability. We're confident that innovative approaches like this will enable us to accelerate access timelines, deliver on our broader commitment to generating leading scientific evidence, and ensure continuous improvement in manufacturing efficiency and optimization."

Novartis also pointed out that the memoranda of understanding which form the basis of the collaboration were already negotiated and signed by The Medicines Company prior to the acquisition. The tie-up with NHS England is part of Novartis's strategy to position inclisiran as an attractive treatment alternative to the under-performing PCSK9 inhibitors already on the market, Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab) and Amgen Inc.'s Repatha (evolocumab). Those drugs are monoclonal antibodies that must be administered every two or four weeks – whereas inclisiran is dosed twice a year – and despite their prices being slashed, Praluent and Repatha have failed to live up to early expectations since their launch in 2015.

In the US, Novartis believes that the two subcutaneous injections of inclisiran a year will be administered in physicians' offices. That means it could be largely reimbursed through medical benefits instead of pharmacy benefits, or Medicare Part B instead of Part D, increasing the attractiveness of the package for payers as well as patients. *(Also see "Novartis Sees Reimbursement Advantage For PCSK9 Launch" - Scrip, 25 Nov, 2019.)*

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J&J To Power Ahead With 10 Launches In Four Years

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Johnson & Johnson has sustained remarkable growth in recent years, and a raft of new products are set to help them maintain this form.

Johnson & Johnson's pharma division looks set to outperform its peers thanks to a portfolio of fast-growing products and up to 10 more new launches between now and 2023.

The company's EVP and worldwide chairman of pharmaceuticals Jennifer Taubert presented an upbeat picture for the 2020-2023 period at the J.P. Morgan conference on 13 January: its medicines division is set to provide the strongest growth for the healthcare conglomerate. J&J has sustained a well above average growth rate for the last eight years – achieving a compound annual growth rate (CAGR) of 8% between 2010 and 2018, compared with the market average of 4.6% in that period.

This has been achieved by stellar growth from newer products such as hemato-oncology medicines Imbruvica (ibrutinib) and Darzalex (daratumumab) plus immunology treatments such as Stelara (ustekinumab) and Tremfya (guselkumab).

Analysts at J.P. Morgan forecast that the company will continue this run over the next five years, although at a lower 5% CAGR.

This will be sustained by the arrival of new products, to include potentially best-in-class BCMA-targeting multiple myeloma CAR-T therapy, JNJ 4528, expected to be filed with the US Food and

TURN TO PAGE 14

Rethinking Patient And Site Engagement

BY DR NUALA MURPHY, PRESIDENT CLINICAL RESEARCH SERVICES, ICON PLC

Drug development costs are increasing annually, with clinical trials identified as one of the most expensive and time-consuming stages of the development process[1]. One factor contributing to this cost inflation is more complex study protocols, which can lengthen trial times while increasing the burden on sites and patients.

Growing complexity is increasingly pervasive. Between 2001-2005 and 2011-2015, the number of endpoints in pivotal Phase III clinical trials almost doubled from seven to 13, according to the Tufts Center[2]. Over the same period, there was also a 70% increase in the total number of procedures performed in typical Phase III pivotal studies. This marked increase in time and effort makes it harder to recruit patients and keep them engaged throughout the trial, which in turn may have a substantial impact on research outcomes and costs[3].

The additional strain on patients from protocol complexity can affect maximizing site engagement and performance as well. Any disconnect between the sites and the protocol design can result in lower patient numbers and sub-optimal trial compliance, which may result in poor data quality and data variability.

In addition to complex designs, protocol amendments create difficulties for trial sites and add to sponsor costs. A study by the Tufts Center for the Study of Drug Development found that almost 50% of substantial protocol amendments are deemed avoidable[4]. Eliminating these amendments could reduce trial times by three months on average, while saving as much as $141,000 and $535,000 spent on substantial protocol modifications for Phase II and III trials respectively, the Center suggested.

It is therefore critical that sponsors proactively address the challenges of clinical-trial design, and consider how to optimize study protocols to boost patient and site engagement, enhance cost-effectiveness, and deliver compelling outcomes for regulators, patients and other stakeholders.

Why Protocol Design Matters

For a clinical trial to produce meaningful results, it must be designed to collect and analyze the right data. Amassing irrelevant data is burdensome to the site and patient and can overcomplicate research efforts, without bringing any real benefits in return.

A study conducted by The Center For Information & Study On Clinical Research Participation (CISCRP) in 2017 estimated that around 30% of data gathered in trials has no influence on any further stages of drug development[5]. The level of focus and investment required to collect unnecessary data would be better directed at more efficient and effective patient recruitment and engagement.

Another key challenge in protocol design is being more scrupulous about selecting endpoints that demonstrate treatment efficacy. Optimizing designs also helps sponsors predict disappointing outcomes at an earlier stage. They can then conserve resources and costs by making timely decisions about terminating trials that fall short of expectations.

A study published in the *Journal of Biopharmaceutical Statistics* in 2016 looked at unnecessary measurements in clinical trials. Typically, these studies have two or more primary endpoints, the authors observed[6]. Each additional endpoint increased medical costs and the number of measurements required. It was observed that it was also likely to result in a longer follow-up period. Furthermore, in any given sample size, the possibility of individual patients exhibiting each of these endpoints could vary widely, adding a further layer of complexity to determining efficacy.

Aside from data issues, there can be lack of alignment between investigators, sponsors and CROs over protocol design. This can have a ripple effect on patient recruitment and retention, since responsibility for patient engagement falls on the site investigator. Improving communication around protocol designs, and making them more patient-centric, ensures that research plans are more appropriate, user-friendly and productive. Exclusively scientist-designed protocols are not in the best interests of patients.

Optimizing Your Protocol

Protocol optimization calls for a combination of strategies, including data analysis, new technologies, and establishing channels for collaboration with patients. By addressing these challenges in clinical-trial design, sponsors will be better equipped to enhance patient recruitment and improve the engagement of patients and study sites alike.

Leveraging new analytical technologies enables mining of data from historical studies to explore potential road blocks in similar protocols. Rather than amending protocols to meet desired endpoints as the trial progresses, sponsors can establish a better-tailored design in advance through an initial review of protocol feasibility from operational, therapeutic and statistical standpoints.

Evidence from successful clinical trials suggests these are often characterized by common themes involving the study site and investigator engagement[7]. Drawing on information collated from other trials, sponsors can develop forecasts that anticipate research outcomes and minimize the need to amend the protocol once the trial is underway.

Contract research organizations (CROs) have access to vast amounts of data from studies conducted over extended periods, across multiple therapeutic areas, and in different indications. This rich repository of data is an effective means of informing and optimizing protocol development, by highlighting any potential hurdles and roadblocks to trial progress.

Patient Input

A research hypothesis with robust, measurable endpoints is meaningless if the sponsor cannot recruit patients or volunteers and retain them over the duration of the trial[8]. A patient-centric recruitment strategy that focuses on motivation and engagement will support more positive outcomes.

Working closely with sites to gain patient feedback through surveys and focus groups to determine perceptions of clinical trial burden and attitudes of the patient experience enables sponsors to potentially amend the protocol in the earlier stages of trial design. These types of patient engagement can be used to develop patient-burden analyses which employ time-in-motion studies to measure the impact of each trial procedure on patients. The analysis can then be used to create a comprehensive matrix specifying the time commitment for each element of the protocol, along with recommendations to enhance patient-centricity. Additional surveys of the target patient demographic can explore attitudes to symptoms, study procedures and visit lengths, as well as their individual and collective influence on patients' willingness to participate in the study.

Involving investigators in review and development of the trial protocol provides another perspective, which could reduce site burden and lead to increased predictability in patient recruitment.

Increased collaboration and communication between the sponsor, patient and investigator is more likely to deliver protocol designs that can be executed more effectively. It will ensure protocols are tailored to answer the right scientific questions, while also empowering investigators to recruit the most suitable and engaged patients.

These insights feed into recruitment and retention strategies that mitigate site and patient burden to drive on-time completion of clinical trials.

Conclusion

Protocol optimization can be instrumental in improving patient and site engagement to mobilize increasingly complex clinical trials. Insights from patients and investigators, coupled with data from historical studies enable sponsors to significantly boost both participant numbers and trial-site compliance.

A laser focus on protocol optimization improves the odds of successful, timely and predictable patient recruitment, while making sure the right data points are collected to deliver cost-effective clinical trials with more compelling study outcomes.

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CONTINUED FROM PAGE 11

Drug Administration in the second half of 2020. *(Also see "J&J Quickly Advances BCMA-Targeting CAR-T As JNJ-4528 Shows 100% Response" - Scrip, 8 Dec, 2019.)*

Following this will be entries into new markets for Janssen, the company's pharma division, including cusatuzumab for acute myeloid leukemia (AML), lazertinib for lung cancer and seltorexant for major depressive disorder.

While none of these new agents will reach the market this year, the company does have an important line extension set for approval, in the shape of a subcutaneous injection of myeloma blockbuster, Darzalex. This will turn its current hours-long infusion time into a five minute injection, an advance which should help the drug carve out an even greater share of its market.

The biggest headwinds facing the company are ongoing lawsuits against it regarding allegations that its talcum powder caused cancer in consumers, and its involvement in opioids marketing: the latter J&J wants to end with a $4bn settlement.

J&J Planned Filings 2019-2023

CANDIDATE	INDICATION	PARTNER
Spravato	Treatment -resistant depression (approved 2019)	In-house
Balversa	Urothelial cancer (approved 2019)	Astex Pharmaceuticals
Cusatuzumab (JNJ-4550)	Acute myeloid leukemia	Argenx
JNJ-4528 BCMA CAR-T	Multiple myeloma	Legend Biotech
Lazertinib JNJ-1937	(EGFR tyrosine-kinase inhibitor) Non small cell lung cancer	Genesco/Yuhan
AAV-CNGB3/CNGA3/RPGR	Retinal disease gene therapy	MeiraGTx
Niraparib (Zejula, PARP inhibitor)	Prostate cancer	GSK/Tesaro
JNJ-7564 GPRC5D/CD3, JNJ-7957 BCMA/CD3	Regimens for multiple myeloma	Genmab
JNJ-6372 EGFR/c-Met (Bispecific EGFR and cMET receptor inhibitor)	Solid tumor	Genmab
JNJ-4500 anti-NKG2D	Crohn's disease	Innate Pharma; Novo Nordisk
RSV Vaccine (Ad26.RSV.preF +preF Protein)	RSV	In-house
Seltorexant JNJ-7922	Adjunctive treatment, MDD	Minerva Neurosciences

BACKING OUT-OF-POCKET COST CONTROLS

The other major area of uncertainty for 2020 and beyond is US pricing and proposed reforms now being debated ahead of November's US elections.

Taubert stuck closely to the industry line that capping and lowering out-of-pocket costs for patients was the best way to reform the system.

The industry is giving its backing to a bipartisan bill from the Senate Finance Committee, which sets out proposals to set an out-of-pocket limit in Medicare Part D.

Industry groups forecast that this would cost the industry $2-3bn a year, but would remove a great deal of the pressure from patients – and also remove political pressure for more aggressive reforms of pharma's current business model.

These include the international reference pricing proposals put forward by President Trump, and the "Medicare for all" plans espoused by Democrat candidates Elizabeth Warren and Bernie Sanders.

"There are elements which I don't think address the fundamental problem which is patient out-of-pocket costs… things such as trying to import foreign price controls," said Taubert. "What that really means is delays and restrictions to access of therapy, [which] I don't think is going to be helpful."

The company is less exposed to the US market than some of its peers, with around 50% of its revenues coming from the US, and 50% non-US markets, and its US revenues split evenly between commercial insurance schemes and government-funded cover including Medicare Part B, Part D or Medicaid.

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O'Day Lays Out Plan For Gilead's Continued HIV Dominance

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Still less than a year on the job, Gilead Sciences Inc. CEO Daniel O'Day knows skeptics question the long-term viability of the firm's dominance in the HIV space. Speaking at the J.P. Morgan Healthcare Conference on 13 January, he asserted that Biktarvy and an investigational capsid inhibitor will enable his company to maintain its status in HIV for years to come.

Despite competition from ViiV Healthcare and other companies, O'Day pointed to Gilead's 14% compound annual growth rate (CAGR) for HIV since 2011, with the period from the third quarter of 2018 to the third quarter of 2019 seeing a 13% growth rate. He also noted Gilead set an industry standard with 15 virology launches in 10 years, including its efforts in hepatitis C and hepatitis B.

O'Day opened his talk by opining that any list of the 10 greatest medical breakthroughs of the decade just ended should include curative regimens for hepatitis C and transforming HIV "from a death sentence to a chronic preventable illness," and the central role Gilead played in those advances.

"What I want to draw your attention to, in addition to the extraordinary HCV revenues that came over the past decade, is the durability of the underlying core business [despite] facing lots of headwinds [and] lots of competition over the past decade," he said.

Approximately eight out of 10 people living with HIV currently are on a Gilead drug, O'Day added.

Gilead doesn't face any crippling patent expirations during the 2020s, the exec continued, but it has been preparing for US patent expiry of its HIV combo pill Truvada (emtricitabine/tenofovir disoproxil fumarate, or TDF) toward the end of 2021. The firm has been working for years to convert patients from regimens that have TDF as a backbone to those containing its second-generation tenofovir alafenamide (TAF), such as Truvada follow-on Descovy (emtricitabine/TAF). Descovy brought in $363m during the third quarter of 2019, and $1.06bn during the first nine months of the year.

For HIV treatment, Gilead projects between 90-95% of patients taking its drugs will be on an emtricitabine/TAF-containing regimen by the fourth quarter of 2020, also including Biktarvy (bictegravir/emtricitabine/TAF), Genvoya (elvitegravir/cobicistat/emtricitabine/TAF) and Odefsey (rilpivirine/emtricitabine/TAF). For PrEP (pre-exposure prophylaxis), the goal is for 40-45% to be on Descovy rather than Truvada by the fourth quarter, up from the current market share of 25%. *(Also see "Biktarvy, PrEP Continue Driving Gilead's HIV Dominance" - Scrip, 3 May, 2019.)* "The market is under-penetrated, and we've got lots of programs to improve that," O'Day said.

Biktarvy and the promise of less-frequent dosing with its capsid inhibitor GS-6207 will enable Gilead to maintain its place at the summit, O'Day said. Biktarvy is now the biggest business at Gilead and is a highly differentiated product with a long patent life ahead, he said. In October, the company reported third quarter sales of $4.2bn for its HIV franchise, up from $3.7bn a year earlier, led by Biktarvy. *(Also see "Gilead Says Sluggish Yescarta Business Will Continue To Fluctuate" - Scrip, 24 Oct, 2019.)* Biktarvy brought in $1.26bn globally during the quarter, including $1.1bn in the US, and $3.17bn during the first three quarters of 2019, including domestic sales of $2.87bn.

"It's the number-one prescribed regimen and it's been growing 80% quarter on quarter since launch and passed the $1bn mark a quarter ago," O'Day said. "This is a strong, durable product, one pill a day with low resistance, high efficacy, is a game-changer in HIV for treatment and will be for years to come."

Through three years of Phase III clinical trial data, there have been zero reports of treatment resistance in patients taking Biktarvy, the CEO said. He also contended that Gilead expects Biktarvy to remain "the preferred treatment option for a majority of [HIV] patients through 2033."

SOME EXPECT HIV FRANCHISE EROSION

Credit Suisse analyst Evan Seigerman maintained a rating of "underperform" for Gilead's stock on 13 January after hearing O'Day's talk, based partly on anticipation of "slowing growth for Biktarvy and forecasted erosion to the HIV platform."

In San Francisco, Gilead CEO O'Day detailed how the company will maintain its dominance in HIV

O'Day also used the J.P. Morgan stage to outline Gilead's current business development strategy, which he said will occur "from a position of strength and a sense of urgency." *(Also see "J.P. Morgan Notebook Day 1: No Big Deals, But Plenty Of Pipeline, Commercial Highlights" - Scrip, 14 Jan, 2020.)* He pointed specifically to the firm's broadened partnership with Galapagos NV as an example of the kinds of deals Gilead will seek moving forward. *(Also see "$5bn Galapagos Deal Won't Be Last For Gilead, Says O'Day" - Scrip, 15 Jul, 2019.)*

"In our view, management has not laid out a concrete strategy for growth, and partnerships and bolt-on acquisitions are unlikely to move the needle near term," Seigerman wrote in response to those comments.

But market research indicates that Gilead may realize a significant opportunity if it can successfully develop its capsid inhibitor GS-6207 to offer patients a variety of dosing options without sacrificing efficacy or safety. O'Day called '6207 "the anchor molecule for what we consider to be less frequent dosing for HIV patients." Gilead is investigating its viability as a weekly oral option and perhaps even a twice-a-year injectable therapy.

Gilead currently is running the Phase II/III CAPELLA study with '6207 in combination with other antiviral therapy in heavily treatment-experienced patients with resistance to prior therapy, the Phase II CALIBRATE open-label study testing '6207 oral and subcutaneous with other antivirals, and a Phase I monotherapy study of '6207 for PrEP.

Data from these studies could enable Gilead to bring a new treatment option to different HIV patient subpopulations, O'Day said. "What's really important is when we go out and talk to those eight out of 10 patients on a Gilead medicine, we ask them what really would make a difference to [them] versus the high bar of one pill once a day," he explained. "What they tell us is they don't want a once-monthly intramuscular injection [but they'll] go once a week oral dose or preferably an injectable that is less frequent, perhaps once a quarter or twice a year."

Gilead is seeking to keep the bar high in HIV, O'Day concluded, and not by seeking merely incremental innovation in that space.

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BioNTech Bags Bargain With Neon Buy

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Wow indeed: Neon sold off very cheap

Germany's BioNTech SE has snapped up struggling US immunotherapy company Neon Therapeutics Inc. for a cut-price $67m.

The all stock deal implies a purchase value of $2.18 per Neon share, which represents a 77% premium on the stock's price on 15 January and following the announcement of the BioNTech deal, shares in the Cambridge, MA-headquartered group jumped 38% to close on 16 January at $1.70. However, these figures are a far cry from the $16 per share that Neon debuted with on the NASDAQ with its initial public offering in June 2018.

Neon has been on the ropes since November last year when it dropped the cancer vaccine NEO-PV-01 after disappointing Phase II data in melanoma, lung and bladder cancers. This prompted a restructuring, resulting in 24% of the workforce being laid off and a decision to focus on two very early-stage compounds.

They are NEO-PTC-01, a personalized neoantigen-targeted T-cell therapy candidate that is Phase I-ready, and NEO-STC-01, which targets shared RAS neoantigens. An investigational new drug submission for the latter, which is initially being developed for pancreatic cancer, is scheduled for 2022.

Ugur Sahin, co-founder and CEO of BioNTech, said the acquisition "fits with our strategy to expand our capabilities and build our presence in the US and further strengthens our immunotherapy pipeline." He added, "I am particularly excited about the adoptive T-cell and neoantigen TCR therapies being developed by Neon, which are complementary to our pipeline and our focus on solid tumors."

ACQUISITION 'CHEAP'

It has been a busy few months for BioNTech which pushed forward with an IPO in October last year despite turbulence in the public markets. The Mainz-headquartered group raised $150m with its NASDAQ entry, well below the $250m that was originally expected and just a few months after it raised $325m via a series B fundraising, smashing the record for the biggest ever private financing round for a European biotech company. *(Also see "BioNTech Fills Coffers With Extra $325m Via Series B Financing" - Scrip, 9 Jul, 2019.)*

Commenting on the Neon deal in a 16 January note, analysts at SVB Leerink said the acquisition was cheap "and carries low-risk from a valuation perspective, considering the recent price surge in BioNTech shares." Adding that it comes with Neon's estimated $30m in cash on hand, the German biotech, the assets "add scale and diversity to BioNTech's own neo-antigen vaccine and CAR-T cell therapy approaches."

The broker also argued that if they stay on, BioNTech would gain experienced executives, including Neon's CEO Hugh O'Dowd and R&D president Richard Gaynor, "who could help build out BioNTech's clinical and commercial presence in the US."

On the flip side, the Leerink analysts stressed that Neon's pipeline was early, "their technology is not validated, initial results from their discontinued neoantigen vaccine program were disappointing, and there is risk of execution distraction of an acquisition and additional clinical asset, as BioNTech enters a critical-period of scaling up a large clinical portfolio." They went on to say that 2020 will largely be about how effectively BioNTech can transition into a company with numerous clinical programs and partnerships to manage."

BioNTech has a notable roster of partners, including Eli Lilly & Co., Genmab AS, Pfizer Inc., Sanofi and Roche. Its pipeline consists of more than 20 product candidates, led by its individualized neoantigen specific immunotherapies (iNeSTs).

The company expects to provide a data update in 2020 from a Phase I trial in multiple solid tumors for BNT122, a Roche-partnered iNeST in combination with the latter's PD-L1 inhibitor Tecentriq (atezolizumab). An update on patient enrolment from a Phase II trial of the drug in first-line melanoma in combination with Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab) is expected in the second half of this year, later than originally forecast.

BioNTech is also conducting a Phase I/II trial of BNT131, its first mRNA-based intratumoral immunotherapy, as a monotherapy or in combination with Sanofi's PD-1 drug Libtayo (cemiplimab). The company also expects to initiate a Phase I/II study for BNT211, which targets a novel solid tumor-specific antigen called Claudin-6, in patients with advanced CLDN6-positive solid tumors in the first half of 2020.

The firm is keen to branch out from its immuno-oncology focus and in September signed an infectious disease collaboration with the Bill & Melinda Gates Foundation. The latter has made an equity investment of $55m as part of the pact that will focus on HIV and tuberculosis. *(Also see "BioNTech Gets Gates Foundation Funding For HIV, TB Drug Discovery " - Scrip, 5 Sep, 2019.)*

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Adaptimmune And Astellas Team Up For Off-The-Shelf T-Cell Therapies

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Hours after Adaptimmune Therapeutics PLC saw its stock soar 200% following a positive presentation at the J.P. Morgan Healthcare Conference in San Francisco, the UK firm has inked a major deal with Astellas Pharma Inc. to develop up to three T-cell therapies.

The Japanese drugmaker's subsidiary Universal Cells Inc. will work with Adaptimmune to develop stem-cell derived allogeneic 'off-the-shelf' T-cell therapies for cancer, having signed a co-development and co-marketing agreement that could be worth up to $897.5m for the Oxfordshire-headquartered group. The deal includes an upfront payment of $50m for Adaptimmune.

The partners will agree on up to three targets and jointly develop T-cell therapy candidates against them using Adaptimmune's capabilities for generating T-cell receptors (TCRs), chimeric antigen receptors (CARs) and human leukocyte antigen (HLA)-independent TCRs. It will also use Astellas's universal donor cell and gene editing technology it obtained through its $102m acquisition of Seattle, WA-based Universal Cells in 2018; Adaptimmune has been collaborating with the latter since 2015.

The Tokyo-based major will fund research until completion of a Phase I trial for each candidate, at which point Astellas and Adaptimmune will decide whether to progress with co-marketing of each candidate or hand over responsibility for further development to the other partner. If a candidate is developed by one company only, the appropriate licenses will become exclusive to them.

As such, the financial terms of the agreement are a bit more complex than usual. Aside from the upfront fee, Adaptimmune could get milestone payments of around $74m for each product if the partnership is co-developed and marketed by both companies.

The UK firm will also get up to $147.5m in milestones per product and up to $110m in sales milestones for those developed unilaterally by Astellas. It will also receive research funding of up to $7.5m per year and tiered royalties on net sales in the mid-single to mid-teen digits.

If it decides not to take on any of the therapies, Astellas could receive $552.5m in similar terms to the Adaptimmune side of the deal. The agreement also allows the companies to share costs of co-development and marketing, with resulting profits split equally.

SPEAR SUCCESS IN LIVER AND MELANOMA

Before the Astellas pact was announced, Adaptimmune got investors excited by using its slot at J.P. Morgan to report that its specific peptide enhanced affinity receptor (SPEAR) T-cell platform has delivered initial responses in four solid tumor indications.

Success with T-cell therapies to date have been in treating blood cancers but Adaptimmune trumpeted two confirmed partial responses (PRs), one in a patient with liver cancer and one with melanoma. The company also reported two unconfirmed PRs – one in a patient with gastro-esophageal junction cancer and one in a patient with head and neck cancer.

Specifically, the confirmed PR (decrease of 100% in target lesions) occurred in a patient with hepatocellular carcinoma data treated in the third cohort of the Phase I ADP-A2AFP trial, while the first patient treated in the low-dose radiation sub-study of the Phase I ADP-A2M4 study with metastatic rectal mucosal melanoma achieved a confirmed PR (decrease of 42% in target lesions).

An unconfirmed PR (decrease of 42% in target lesions) was seen in the first patient with metastatic gastro-esophageal junction cancer treated in the first cohort of the next-generation SURPASS trial. The second unconfirmed PR (decrease of 36% in target lesions) was in a patient with head and neck cancer treated in the expansion phase of the aforementioned ADP A2M4 study

Adaptimmune CEO Adrian Rawcliffe said the responses demonstrated that the SPEAR platform was "clearly active and can overcome the challenges of treating a range of solid tumors with a T-cell therapy product. There continues to be a favorable benefit/risk profile for all products and indications under study."

He acknowledged that "these are early results and we need more patient data and durability information to determine which therapies to develop. Nonetheless, this is…a validation of the importance of our proprietary affinity engineering."

Analysts at SVB Leerink issued a note on 13 January saying that demonstrating anti-tumor activity in indications other than synovial sarcoma represents an important update." Last month, the company received regenerative medicine advanced therapy designation from the US Food and Drug Administration for ADP-A2M4 for synovial sarcoma based in part on the expansion phase of the Phase I trial with 13 out of 14 patients showing clinical benefit; Adaptimmune hopes to get to market for that indication in 2022.

However Leerink warned that "despite the promising headline, these results remain extremely early and we caution on getting overly excited until additional patient data and durability information are provided."

Regardless of the broker's caution, shares in the NASDAQ-quoted biotech, which has facilities in Philadelphia, PA as well as in Oxford, closed up 200% on 13 January to $3.99.

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MorphoSys Chooses Incyte As Its Global Tafasitamab Partner

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In a pact widely welcomed by investors, MorphoSys AG and Incyte Corp. have inked a global collaboration and license pact to further develop and commercialize MorphoSys's anti-CD19 antibody tafasitamab, formerly known as MOR208, which is in clinical development for the treatment of B-cell malignancies such as diffuse large B-cell lymphoma and chronic lymphocytic leukemia.

The alliance was announced on 13 January and provides MorphoSys a partner with considerable experience in hematology and oncology. Incyte in turn gets access to a novel compound that could help reduce reliance on its flagship JAK inhibitor, Jakafi (ruxolitinib).

DEAL DETAILS

The deal calls for MorphoSys to receive an upfront payment of $750m. Incyte will make an equity investment into MorphoSys of $150m through the purchase of new American Depositary Shares (ADS) in MorphoSys. MorphoSys will be also eligible to receive milestone payments amounting to up to $1.1bn.

"The deal is commercially very attractive for MorphoSys," analysts at Commerzbank said in a same-day reaction note.

Analysts at Bryan, Garnier & Co agreed, adding in a reaction note to investors that "Incyte is a perfect match for Tafa(sitamab)."

"Today's deal is bound to unlock the full potential of tafasitamab," analysts at Kempen predicted in their initial reaction to the news.

MorphoSys is evaluating tafasitamab as a therapeutic option in B-cell malignancies in a number of ongoing combination trials.

At the end of December, MorphoSys submitted a biologics license application to the US Food and Drug Administration for tafasitamab for the treatment of relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

The compound received breakthrough therapy status from the FDA in October 2017 based on positive results from the open-label Phase II combination trial, called L-MIND, investigating the safety and efficacy of tafasitamab in combination with lenalidomide in patients with r/r DLBCL who are not eligible for high-dose chemotherapy and autologous stem cell transplantation. *(Also see "MorphoSys Targets 2020 Tafasitamab Launch Following Good DLBCL Data" - Scrip, 17 May, 2019.)*

News of the global collaboration comes less than six months after Jean-Paul Kress took the helm at MorphoSys as its new CEO from Simon Moroney, the firm's founder and CEO for 27 years, who built up the firm's antibody R&D expertise. *(Also see "MorphoSys: A European Champion Crossing The Biopharma Rubicon" - In Vivo, 9 Oct, 2019.)*

Kress's remit when taking the CEO role was to turn the German group into a truly commercial biopharma company. The global partnership with Incyte promises to fit that bill, analysts said.

"The combination of our strong antibody and drug development expertise partnered with Incyte's well-established hematology-oncology experience and their commercial operations in key territories has the potential to significantly broaden the tafasitamab opportunity," Kress said.

TAFASITAMAB TESTING

Both parties have agreed to co-develop tafasitamab broadly in r/r DLBCL, frontline DLBCL as well as additional indications beyond DLBCL, such as follicular lymphoma (FL), marginal zone lymphoma (MZL) and chronic lymphocytic leukemia (CLL).

Incyte will be responsible for initiating a combination study of its investigational PI3K-delta inhibitor parsaclisib and tafasitamab in r/r B-cell malignancies. Incyte will also be responsible for leading any potential registration-enabling studies in CLL and a Phase III trial in r/r FL/MZL.

MorphoSys will continue to be responsible for its currently ongoing clinical trials of tafasitamab in non-Hodgkin's lymphoma, CLL, r/r DLBCL and frontline DLBCL.

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NICE Draft Guidance: Rejects Keytruda In Head & Neck Cancer, Xospata In AML

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The UK's National Institute for Health and Care Excellence has rejected several anticancer agents, and indicated that local clinical practice has still to be taken into account when introducing medicines – decisions which may act as a reality check to biotech and pharmaceutical companies. The decisions include the rejection of the use of Merck & Co. Inc.'s Keytruda (pembrolizumab) as a first-line therapy in head and neck cancer in draft guidance, rejection of Astellas Pharma Inc.'s Xospata (gilteritinib) in acute myeloid leukemia in draft guid-

ance, and termination of the appraisal of Roche's Tecentriq (atezolizumab) with carboplatin and nab-paclitaxel for untreated advanced non-squamous non-small cell lung cancer. However, there were recommendations in additional settings for AstraZeneca PLC/MSD's Lynparza (olaparib) and Pfizer Inc.'s Ibrance (palbociclib).

The 15 January decision by NICE to reject, in draft guidance, the use of Keytruda as a first-line therapy for head-and-neck cancer has attracted particular opprobrium from leading local cancer researcher Kevin Harrington, professor of biological cancer therapies at the Institute of Cancer Research, for its effect on patients. Harrington was lead investigator in the UK arm of the KEYNOTE-048 study of pembrolizumab in head and neck cancer patients.

Gaining a positive health technology assessment (HTA) decision may also be of particular importance for Merck & Co, which has a lead over rivals in this therapeutic segment - Keytruda became the first checkpoint inhibitor to be approved in the EU at the end of last year in the first line setting of metastatic or unresectable recurrent head and neck cancer.

A similar but slightly broader indication was approved for Keytruda in the US in the middle of 2019, and other checkpoint inhibitors and investigational anticancers are in clinical development for head and neck cancer.

DRAFT GUIDANCE

NICE says in its draft guidance that separate clinical evidence was not provided by Merck on the use of Keytruda in patients whose cancers started inside and outside the mouth; information on the cost effectiveness of Keytruda in the two different patient groups was therefore incomplete.

The distinction is important, according to NICE, because in the UK, clinical practice dictates that if the cancer is inside the mouth, it is usually treated with cetuximab, platinum chemotherapy and 5-fluoruracil. If the cancer is outside the mouth, cetuximab is omitted. But in the KEYNOTE-048 study, Keytruda alone or combined with platinum chemotherapy and 5-FU was compared with cetuximab, platinum and 5-FU, regardless of the location of the cancer.

In KEYNOTE-48, pembrolizumab extended overall survival compared with the comparator group, but the NICE draft guidance says patients in the study may have been in better condition than those in the UK at this point in their disease. And even though Merck pointed out that a post hoc analysis based on cancer location was not prespecified in the study, NICE's committee said it would still like to see clinical effectiveness analyses in the two subgroups.

Harrington was scathing about the delay. "There is clear evidence that pembrolizumab has survival benefits for patients with head and neck cancer, and it is also a much kinder treatment than intensive chemotherapy," he commented.

"Patients will have to wait even longer before they can access this immunotherapy as the first treatment of choice for advanced head and neck cancer." He urged NICE to urgently revisit the evidence, and to work with Merck on a suitable compromise that would make Keytruda available to these patients as soon as possible.

Keytruda was approved in the EU in November 2019 for use as monotherapy or with platinum and 5-FU chemotherapy for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumors express PD-L1 with a combined positive score (CPS) of 1 or more.

OTHER REJECTIONS

Also on 15 January, NICE reported it was not recommending Astellas's FLT3 inhibitor Xospata for treating relapsed or refractory FLT3 mutation-positive acute myeloid leukemia in adults, even though AML is an aggressive leukemia which requires immediate treatment, and as an oral therapy Xospata can be taken at home and may improve quality of life by enabling patients to avoid chemotherapy.

In draft guidance, the institute said there was uncertainty around long-term survival, even though Xospata can increase life expectancy by more than three months compared with current therapies, and it estimated an ICER for Xospata of more than £90,000 per QALY gained.

Xospata was approved by the EU Commission in October 2019, after an accelerated review. A potential rival, Daiichi Sankyo Co. Ltd.'s Vanflyta (quizartinib), is also eyeing the AML market.

WRONG SETTING FOR TECENTRIQ

NICE said it was unable to make a recommendation on Roche's checkpoint inhibitor, Tecentriq (atezolizumab), combined with carboplatin and nab-paclitaxel for untreated advanced non-squamous small-cell lung cancer, because the company did not provide an evidence submission.

However, Roche explained the combination was unlikely to be used at this point in the treatment pathway. Tecentriq has several NICE recommendations in different settings in NSCLC.

LYNPARZA, IBRANCE RECOMMENDED

On a more positive note, NICE recommended AstraZeneca/MSD's Lynparza (olaparib) as a later-line option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, in final guidance released on 15 January.

In one setting, Lynparza will be routinely available in the NHS, and in another it is recommended for use within the Cancer Drugs Fund. The drug was recommended by NICE earlier in the treatment pathway in the middle of last year.

And finally, Pfizer's CD4/6 inhibitor, Ibrance (palbociclib), has caught up with rival CDK4/6 inhibitors in the UK, and is now recommended in combination with fulvestrant for use via the UK Cancer Drugs Fund as an option for treating hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy.

The final guidance, released on 15 January, notes that final overall survival data with the palbociclib/fulvestrant combination are not yet available, and cost-effectiveness estimates are also uncertain, so the combination cannot be recommended for routine use in the NHS.

Other CDK4/6 inhibitors, Novartis AG's Kisqali (ribociclib) and Eli Lilly & Co.'s Verzenios (abemaciclib), have already been placed in the Cancer Drugs Fund for the second-line indication.

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Recordati's Isturisa Approved For Cushing's In EU

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Recordati Industria Chimica & Farmaceutica SPA has been given the green light from the European Commission to market Isturisa, the Cushing's syndrome drug it acquired from Novartis AG as part of a $390m deal inked with the Swiss major in July last year.

Flags out for Isturisa approval

Isturisa (osilodrostat) is a cortisol synthesis inhibitor which works by inhibiting 11-beta-hydroxylase, an enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. The approval, which follows a positive opinion in November from the European Medicines Agency's drug evaluation committee, the CHMP, was primarily based on data from the LINC-3 study.

The trial demonstrated that a significantly higher proportion of patients in the Isturisa arm maintained normal mean urinary free cortisol (mUFC) at week 34 versus placebo (86.1% vs 29.4%). Cortisol level control is the primary objective in the treatment of Cushing's, a rare disorder where the body produces too much corticosteroid hormone; it leads to patients experiencing weight gain, fat build-up on the face and bruising.

The reductions in mUFC were accompanied by weight, waist circumference, glucose and blood pressure improvements, as well as improved quality of life and depression scores. Isturisa was also generally well tolerated in the LINC-3 study.

The Italian firm will also benefit from the tablet having orphan drug status in Europe, which provides 10 years of market exclusivity. CEO Andrea Recordati said the company was aiming to make the available worldwide "and the European approval and subsequent launch is an important first step in this direction."

The July 2019 deal also gave Recordati access to Signifor (pasireotide) and its long-acting version Signifor LAR. The latter two, which had sales of $72m in 2018, are also approved to improve the symptoms of Cushing's as well as acromegaly in adults for whom surgery is not an option.

As the Isturisa approval was announced, analysts at Credit Suisse issued a note saying that "we see risks into the company's expansion into endocrinology", claiming that Recordati "has limited experience in launching new specialty products." The Milan-headquartered group told *Scrip* that it will be beefing up its commercial organization in Europe, noting that the first launch will be in Germany in the third quarter of this year. However the 16 January note was reasonably positive on the whole, with Credit Suisse stating that Recordati has "a very strong EU infrastructure that has proved capable of absorbing more products which can then be marketed to re-establish what would typically have been a declining brand for the previous owner."

In July 2018, a consortium of private equity funds led by CVC took a controlling stake in Recordati, founded in 1926, for €3.03bn, at a sharp discount to the company's share price. Credit Suisse noted that with the new owner "and new chairman Fleming Ornskov, who has an acquisitive record, investors appear to be expecting more deals." Ornskov, who orchestrated Shire PLC's $32bn takeover of Baxalta Inc. in 2016 then sold the company to Takeda Pharmaceutical Co. Ltd. for $62bn a year ago before taking over as Galderma's CEO, became chairman of Recordati in February 2019.

As for the plans for Isturisa in the US, the therapy has a Prescription Drug User Fee Act date in March this year and the company hopes to launch in 2022 at the latest. However, on the company's third quarter 2019 investor call, CEO Recordati spoke about "a lack of clarity" as to whether the US Food and Drug Administration would require the firm to submit data from the ongoing LINC-4 study which is still being managed by Novartis and is not due to read out before the second half of 2020. He added that the company expected peak sales of over $100m.

COMPETITION FROM STRONGBRIDGE

If all goes well with the FDA, Recordati could steal a march on a rival Cushing's treatment developed by Ireland-domiciled and US-headquartered firm Strongbridge Biopharma PLC. Topline results from the firm's Phase III LOGICS study of Recorlev (levoketoconazole) are expected in the second or third quarter of 2020.

Last week (9 January) Strongbridge noted that the trial was more than 70% enrolled and it expected to submit a new drug application to the FDA approximately six months after reporting the topline LOGICS results. Recorlev, which is also a cortisol synthesis inhibitor with orphan drug designation from the FDA and the EMA, is the 2S, 4R enantiomer of ketoconazole (Johnson & Johnson's Nizoral and generics), which mainly has been used as an antifungal but is also used off label in Cushing's, although it has a black-box warning for potentially fatal liver toxicity.

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AbbVie's Skyrizi Tops Novartis's Cosentyx In Psoriasis Contest

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In another study showing the superiority of IL-23 inhibition to IL-17 inhibition for treating psoriasis, AbbVie Inc. 's Skyrizi in a Phase III trial bettered Novartis AG's Cosentyx by meeting both primary and all secondary endpoints in adults with moderate-to-severe plaque psoriasis.

AbbVie on 14 January said Skyrizi (risankizumab) met both primary and all ranked secondary endpoints, including superiority at week 52, versus Cosentyx (secukinumab) in the 327-patient head-to-head study, demonstrating significantly higher rates of skin clearance compared with the IL-17 agonist.

HEAD-TO-HEAD HEADLINES

The results showed 87% of Skyrizi-treated patients achieved 90% skin clearance (PASI 90) at week 52 compared with 57% of those receiving Cosentyx, one of the primary endpoints ($p<0.001$), the company said. The trial also met the other primary endpoint of non-inferiority to Cosentyx, with 74% of Skyrizi patients achieving 90% skin clearance at week 16 versus 66% for Cosentyx.

Skyrizi also showed superiority to Cosentyx on all ranked secondary endpoints. Skyrizi's safety profile was consistent with that observed in previously reported studies, with no new safety signals observed, AbbVie added.

Analysts said the study should enhance the commercial prospects of AbbVie's Skyrizi, a second-to-market IL-23 inhibitor for plaque psoriasis behind Johnson & Johnson's Tremfya (guselkumab).

Skyrizi was approved in the US in April or moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. *(Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - Scrip, 24 Apr, 2019.)* The IL-23 antagonist, which is also approved in Europe Japan and Canada, generated sales of $91m in the third quarter of 2019.

Observers says AbbVie's capabilities in immunology and skin disorders as demonstrated with Humira (adalimumab) provide Skyrizi with a clear competitive advantage which should help it jockey for position against J&J's IL-23 inhibitor Tremfya as well as IL-17 rivals such as Eli Lilly & Co.'s Taltz (ixekizumab) and Cosentyx.

Novartis's big-selling drug Cosentyx saw sales climb 25% year-over-year to $937m in the third quarter of last year. The IL-17 antagonist, which is approved for adults with moderate-to-severe plaque psoriasis, active psoriatic arthritis and active ankylosing spondylitis, looks set to greatly expand its range of indications over the next decade. *(Also see "Novartis Targets Ten Indications For Cosentyx " - Scrip, 6 Dec, 2019.)*

Still, Cosentyx was also topped in a head-to-head study in 2018, with Johnson & Johnson's IL-23-targeted biologic therapy Tremfya showing superiority in treating adults with moderate-to-severe plaque psoriasis. *(Also see "ECLIPSE: J&J's Tremfya Beats Novartis' Cosentyx For Long-Term Psoriasis Clearance" - Scrip, 12 Dec, 2018.)*

And in November Cosentyx narrowly failed to show superiority over AbbVie's Humira in a late-stage psoriatic arthritis study. *(Also see "Novartis's Cosentyx Fails To EXCEED Humira in PsA " - Scrip, 1 Nov, 2019.)*

Analysts said the competition – and debate - looks set to intensify after the latest head-to-head trial.

"This is another study confirming the superiority of IL-23 inhibition to IL-17 inhibition as a treatment strategy in psoriasis," Leerink analysts said in a reaction note to investors on 14 January.

The brokerage predicted in a 14 January commentary that Skyrizi would consequently become a "mega blockbuster."

"Skyrizi in particular offers the advantage of long-term three-monthly dosing, compared to monthly dosing with Cosentyx and Taltz."

Leerink concluded. "Today's positive head-to head trial result increased our conviction that Skyrizi will continue to grow strongly and gain share from its competitors."

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AZ Halts Epanova Study As High Placebo Effect Kills Acasti's Omega-3 TRILOGY-1 Trial

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AstraZeneca PLC's hopes of emulating Amarin Corp. PLC's Vascepa with its omega-3 product Epanova have been hit just as commercial prospects were put on hold for Acasti Pharma Inc.'s similar product CaPre after a late-stage study in severe hypertriglyceridemia failed to meet its primary endpoint.

AstraZeneca said it was closing the Phase III large-scale cardiovascular (CV) outcomes trial STRENGTH of Epanova (omega-3 carboxylic acids) on the recommendation of an independent data monitoring committee due to its low likelihood of demonstrating a benefit to patients with mixed dyslipidemia (MDL) who are at increased risk of CV disease.

The disappointment came with a financial hit. AstraZeneca is reviewing its

TURN TO PAGE 23

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, 10–16 JANUARY 2020

Event Type	Lead Company	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	AstraZeneca/BMS	anifrolumab	Systemic Lupus Erythematosus	NEJM, 16 January, 2020	-	-
Phase III Published Results	Cara Therapeutics	Korsuva (difelikefalin)	Pruritus	NEJM, 16 January, 2020	-	-
Phase III Updated Results	Resverlogix Corporation	apabetalone	CV Events In Diabetes	BETonMACE; Positive Results	0	23
Phase III Top-Line Results	Akari Therapeutics, Plc	Coversin (nomacopan)	Paroxysmal Nocturnal Hemoglobinuria	CAPSTONE; Positive Interim Data	2	62
Phase III Top-Line Results	Acasti Pharma, Inc.	CaPre (omega-3 phospholipid)	Hypertriglyceridemia	TRILOGY 1; Mixed Results	-10	37
Phase III Top-Line Results	Axsome Therapeutics, Inc.	AXS-14 (esreboxetine)	Fibromyalgia	Met Primary Endpoints	52	52
Phase III Trial Initiation	Akcea Therapeutics/Ionis	AKCEA-TTR-LRx	TTR-Mediated Amyloid Cardiomyopathy	CARDIO-TTRansform; CV Outcomes	0	62
Phase III Trial Initiation	Abeona Therapeutics, Inc.	EB-101, gene therapy	Epidermolysis Bullosa	VIITAL; Autologous Cell Therapy	38	68
Phase III Trial Initiation	Cerevel Therapeutics, LLC	tavapadon	Parkinson's Disease	TEMPO-1,2,3; Across Disease Stages	35	57
Phase III Trial Initiation	Ark Biosciences	ziresovir	RSV Infection	In Children In China	0	27
Phase II/III Trial Initiation	Cortexyme, Inc.	COR388	Alzheimer's Disease	GAIN Extension; GingipAIN Inhibitor	0	52
Phase III Trial Announcement	Iveric bio, Inc.	Zimura (avacincaptad pegol)	Dry Age-Related Macular Degeneration	ISEE2008; Complement C5 Inhibitor	0	24

Source: Biomedtracker | Informa, 2020

CONTINUED FROM PAGE 21

$533m current value of the intangible asset, and is taking a $100m write down on inventory. Any impairment will be treated as a non-core item in the fourth quarter of 2019, it said.

Epanova is approved in the US and indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridaemia, which is not affected by the data from the STRENGTH trial, AstraZeneca noted. The company gained the product via its acquisition of Omthera Pharmaceuticals in 2013, when the product was approaching the approval stage for the initial indication. AstraZeneca had hoped that CV outcomes success would have propelled it to blockbuster status.

STRENGTH was comparing the effect of Epanova 4g daily with corn oil placebo on reducing the risk of major adverse cardiovascular events (MACE) in patients on optimal statin therapy with mixed dyslipidaemia and at high risk for CV disease. A total of 13,086 patients had been enrolled and the full data will be presented at a forthcoming medical meeting, AstraZeneca said.

PLACEBO 'KRILLLER'

Acasti's CaPre is a purified omega-3 phospholipid concentrate derived from krill oil. It is being developed to treat high levels of triglycerides in the blood, a metabolic condition that contributes to increased risk of cardiovascular disease and pancreatitis.

But CaPre's effectiveness was put in doubt after TRILOGY 1 data showed a high placebo effect, cancelling out the drug's effectiveness in the trial.

Top-line results from TRILOGY-1 were released on 13 January and showed CaPre reduced triglycerides by 30.5% and 36.7% at 12 weeks and 26 weeks in patients, an impressive outcome that was effectively neutralized by triglyceride reductions of 27.5% and 28.0% in patients on placebo.

The study had been seeking a 20% difference in triglyceride reduction versus placebo, an endpoint TRILOGY-1 failed to meet because of the "unprecedented" high placebo effect seen at five testing sites, the company said.

TRILOGY-1 was a randomized, double-blind study that compares 4g of CaPre daily against placebo in 242 patients with severe hypertriglyceridemia at a total of 54 enrolling sites. The placebo used in the trial was simple cornstarch.

"While we are encouraged by the magnitude of reduction in triglyceride levels seen among patients receiving CaPre, the large placebo effect was completely unexpected, and was about double what was seen in all other therapeutic omega-3 hypertriglyceridemia trials," said Jan D'Alvise, president and CEO of Canada-based Acasti.

The topline line trial results also confounded investors, who sought shelter in the confusion by selling Acasti stock, causing its price to plummet.

Analysts reacted by putting the Canadian biotech's prospects under review. "The high placebo response in TRILOGY-1 came as a surprise to us as cardiovascular trials normally do not usually have this issue," analysts at Mackie Research said in a same day note to investors.

Acasti said a full audit of enrolling sites, including review of all raw data and records from patients taking both CaPre and placebo, would now be conducted to identify a possible main cause for the high placebo effect.

Published online 14 January 2020

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Joseph Camardo	ADC Therapeutics SA	Head, Medical Affairs	Celgene Corp	Senior Vice President, Celgene Global Health	10-Jan-20
Andreas Harstick	Affimed Therapeutics AG	Chief Medical Officer	Molecular Partners AG	Chief Medical Officer	1-Mar-20
Kevin Ostrander	BioDelivery Sciences International	Senior Vice President, Business Development	Glenmark Pharmaceuticals	Head, North America Business Development	6-Jan-20
Michelle Robertson	Editas Medicine Inc	Chief Financial Officer	Momenta Pharmaceuticals Inc	Chief Financial Officer	9-Jan-20
Han Myint	NexImmune Inc	Chief Medical Officer	Celgene	Vice President, Global Medical Affairs	8-Jan-20
John Trainer	NexImmune Inc	Chief Financial Officer	MedImmune	Vice President and Head, Partnering and Strategy	8-Jan-20

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

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