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BMS/Celgene Does Not Portend Hectic M&A Year, Says EY

JOSEPH HAAS joseph.haas@informa.com

Bristol-Myers Squibb Co.'s $74bn acquisition of **Celgene Corp.** doesn't necessarily portend a hectic year of biopharmaceutical M&A, according to EY Global Life Sciences Transaction Leader Peter Behner, nor does **Eli Lilly & Co.**'s $8bn purchase of **Loxo Oncology Inc.** – but weighing transformational M&A versus bolt-on deals, he predicts more of the latter.

Interviewed during the J.P. Morgan Healthcare Conference Jan. 8, where EY released its 2019 *M&A Firepower Report* estimating the M&A capacity of the life sciences sector, Behner pointed out that the same factors that held down biopharma M&A in 2018 still apply. Potential buyers remain in hold mode due to what they perceive as high valuations for the available companies and assets as well as concerns about geopolitical uncertainties, such as the pricing environment in the US, he said.

If the stock market remains stable, the valuation situation will remain static for now, Behner said. "Therefore, high valuations, which were a reason [for M&A sluggishness] last year, are still a reason now," he said. "Interest rates in the US have gone up, Europe is drying up its liquidity despite the fact that they haven't raised interest rates yet. So, deals do get a bit more expensive, although it's not dramatic. … That's why we're projecting that 2019 will be similar to last year."

Still, EY's projections are for one or two major biopharma M&A deals this year, and if a second of the magnitude of Bristol/Celgene occurs in 2019, the aggregate M&A numbers are fairly certain to rise, he conceded. Bristol agreed to pay $74bn to acquire the big biotech on Jan. 3, enhancing its oncology and immunology businesses and making it the seventh-largest biopharma company globally. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)* It was the third-largest biopharma M&A deal by value in industry history, and Behner noted that another deal in that range would put the industry three-quarters of the way to last year's M&A total of $198bn. *(Also see "Bristol/Celgene A Record-Setting Merger, If It Happens" - Scrip, 3 Jan, 2019.)*

But, the factors that made sense for a Bristol/Celgene combination might not easily be repeated in biopharma, he said. "There were in my opinion clear reasons why this deal made sense," Behner explained. "Celgene's stock price had come down dramatically, so the valuation argument was gone and the deal for these two companies seemed to make perfect sense. It's like all the puzzle pieces coming together from a portfolio point-of-view; it strengthens both companies tremendously in my opinion, it creates significant scale for the combined firm in oncology and it catapults them to being the number-one or two company [in cancer] depending on which year you look at."

BOLT-ON DEALS LIKELY THE NORM AGAIN IN 2019

So for now, he cautioned, it might be best to view Bristol/Celgene as an outlier, while a smaller acquisition like the $8bn Lilly/

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from the editor

eleanor.malone@informa.com

January is a particularly busy time of year for crystal ball gazers. After a couple of years of overzealous New Year prophesying in the M&A arena, industry watchers appear to be more cautious this year. Even after Bristol-Myers Squibb started 2019 by announcing the third-largest acquisition in pharma history, EY is taking a measured approach, viewing this deal as a likely outlier in 2019 (rather as Takeda/Shire, which closed last week, was in 2018). "Bolt-on" remains the buzzword (see cover story).

January is also a time to look back, and while M&A activity was muted in 2018, the true business of pharma – getting drugs to market – was brisk. The EU's tally of 42 new active substance approvals far outstripped the 29 new substances approved in 2017, while in the US the FDA gave the green light to a record-breaking 65 novel drugs, up from 46 in 2017.

On the topic of celebrating 2018 achievements, some of you may have trumpets of your own to blow. If you work in R&D and are proud of what you did last year, have you considered entering the Clinical and Research Excellence (CARE) Awards hosted by *Scrip*'s sister business Citeline? Categories cover different aspects of drug development and clinical trial activity, from early phase research to major pivotal studies, with prizes for the best clinical research team of the year, most innovative clinical trial design, process innovation and more. The entry deadline has been extended to January 25, so head to pharmaintelligence.informa.com/events/awards/care-awards-2019 to find out more and submit your entry.

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EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
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exclusive online content

Anticancers, Orphans & The First CAR-Ts: New EU Drug Approvals In 2018

IAN SCHOFIELD ian.schofield@informa.com

2018 was a bumper year for new drug approvals in the EU, with 45 products containing a total of 42 new active substances authorized for marketing, well up over the 2017 total of 28 products containing 29 new active substances.

Orphan-designated medicines also put in a strong showing, with the number of approvals more than doubling to 17, compared with just eight a year earlier.

The last time this kind of tally was seen was in 2015, when products containing a total of 46 NAS were authorized for marketing, of which 16 were for orphan indications. The figures are drawn from the European Commission's register of centralized marketing authorizations (as of Jan. 8, 2019) and from Informa's regularly updated new drug approvals tracker. *(Also see "New EU Approvals" - Pink Sheet, 30 Nov, 2018.)*

Anticancer medicines topped the EU approvals table in 2018, with 11 marketing authorizations, followed closely by drugs for infectious diseases (nine) and metabolism/diabetes (eight).

The oncology approvals included the first two CAR-T cell medicines, Novartis's Kymriah and Gilead Sciences' Yescarta, both of them orphan therapies for blood cancers.

Among new medicines in other therapeutic categories that made a splash last year were Roche's multiple sclerosis therapy, Ocrevus, and Spark Therapeutics' orphan drug Luxturna for inherited retinal dystrophy.

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Loxo deal might be more typical of what will occur in 2019 – though the oncology-focused acquisition would have been the sixth largest transaction of 2018. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)*

In 2018, bolt-ons comprised 81% of deal volume and 43% of total deal value in the life sciences, EY reported. Of executives in its latest survey, only 3% cited a focus on major M&A in the coming year, while more than 70% said they hoped to make deals that offer product-focused innovations or portfolio optimization.

"I would say we're off to a great start this year, but that doesn't necessarily mean there's going to be another mega-deal this year," he said. "And if there isn't another mega-deal this year, then we're probably still in the [2018] window. Now, when you run around [this conference] and talk to people, there is rumor of a bunch of other smaller deals, bolt-on deals being in the hopper and probably coming in the next couple of days, so that's all good stuff. But again, it would not indicate that this will be an exceptional year."

M&A activity has declined since 2014 as a percentage of the industry's firepower, according to EY, due largely to the concurrent increase in valuations for the kinds of smaller companies that typically get acquired. EY defines "firepower" as a company's individual or industry's aggregate capacity to do M&A based on balance sheet strength. Inclusive of big pharma, big biotech and medtech, the life sciences sector had a combined M&A firepower of $1.2 trillion in 2018, but used only 16% for M&A activity, the report states. In 2014, the life sciences sector deployed 27% of its firepower on M&A.

EY's survey of 22 life sciences executives showed that 68% cited high valuations and 62% mentioned geopolitical uncertainty as the primary factors that held back large deal-making in 2018. Behner said "geopolitical uncertainty" is a vague phrase, but likely indicates concerns about the drug pricing environment both in the US and globally; the slowing down of the economy in China, now the world's second-largest market for prescription drugs; and the potential complications of the UK's pending departure from the EU, i.e., Brexit.

"When you look at the concerns that pharma executives have, number one is pricing," Behner told *Scrip*. "That's anywhere in the world. The US probably is the single-most important so clearly there's that focus in the US, but it's a global question. Most governments are concerned about this and talk about this, and pharma companies would rather talk about value than prices."

"I would say we're off to a great start this year, but that doesn't necessarily mean there's going to be another mega-deal this year," he said.

China's roaring economy, while still strong, is showing signs of cooling off and that poses worry for biopharma companies too since the second-largest market is also largely an out-of-pocket market for pharmaceutical products, he added. "An economic crisis or cooling would have an effect on people's ability to buy drugs or pay for drugs, so that's clearly another concern," he said.

THERAPEUTICALLY FOCUSED FIRMS DO BETTER IN GENERAL

Another finding of EY's report was that of the 25 largest biopharma companies, those that are more focused – meaning they derive 50% of sales or more from one therapeutic area – perform better on classical financial measures than unfocused companies.

For this reason, Behner thinks Bristol's buyout of Celgene has very strong rationale. EY sees Bristol, despite its pioneering position in immuno-oncology, as lacking therapeutic focus and strong growth prospects. Celgene, meanwhile, should bolster the pharma in both areas, adding its hematology portfolio and bolstering a combined pipeline that should offer six new approvals in the next 12-24 months.

Since 2014, according to EY's research, more-focused biopharmas have enjoyed 40% EBITDA (earnings before interest, tax, depreciation and amortization) growth on average, compared to 28% for unfocused companies. The five-year compound annual growth rate is 14% for the focused entities and 2% for the unfocused, it found, while return on investment saw a five-year average of 14% for focused companies and 3% for unfocused ones. Meanwhile, valuation as measured by enterprise value to revenue multiple was 5x for focused companies, 4.1x for unfocused companies.

EY sees the best rationale for major M&A for **Eisai Co. Ltd.**, **Boehringer Ingelheim GMBH**, **Sanofi**, **Merck & Co. Inc.**, **Novartis AG**, **Astellas Pharma Inc.**, **Pfizer Inc.** and **Daiichi Sankyo Co. Ltd.**. Pfizer is often at the center of M&A speculation, but incoming CEO Albert Bourla reiterated during a JPM talk on Jan. 7 that it is not seeking such a transaction. *(Also see "J.P. Morgan Notebook Day 1: Pfizer, Gilead, Alnylam, Novartis, Sarepta, Deal Trends And Cell Therapy Challenges" - Scrip, 8 Jan, 2019.)*

For companies not in the low-growth/therapeutically unfocused "bucket," EY says bolt-on deals make greater sense in the near term. "For the other buckets, we recommend the bolt-on deals," Behner said, "always with the assumption that mega-deals are somewhat disruptive. It takes a couple of years to integrate, you're losing a lot of talent, you eventually get re-focused in the market, there are all sorts of issues related to that. And the other impact obviously is that if you think about how valuations are high, then yields become diluted to your existing shareholders. If the market thinks you're overpriced, consequently your stock price goes down, which is in fact what happened to Bristol."

Bolt-on deals offer growth potential with lesser downside in terms of stockholder dilution, he said, making for safer bets. Companies with therapeutic focus and better growth prospects can look to these less-risky transactions for potential progress.

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Lift-Off For Lilly In Cancer Genetics With Loxo Buy

KEVIN GROGAN kevin.grogan@informa.com

A second major pharma-biotech merger plan has landed in the space of a few days, following on from the proposed $74bn acquisition of **Celgene Corp.** by **Bristol-Myers Squibb Co.**, with **Eli Lilly & Co.** agreeing to pay $8bn to buy the closely watched tumor agnostic specialist **Loxo Oncology Inc.**

Lilly is paying a whopping $235 per share in cash to get hold of Loxo, which represents a premium of 68% to the latter's closing stock price on Jan. 4. The deal announced on Jan. 7 as the annual J.P. Morgan Healthcare Conference got under way in San Francisco represents a major push by Lilly into cancer genetics, and it is expected to close by the end of the first quarter. If Loxo decides to pull out, the latter will be required to pay a termination fee of $265m.

For its money, the Indianapolis-headquartered major is getting hold of Loxo's pipeline of targeted medicines focused on cancers that are dependent on single gene abnormalities that can be detected by genomic testing. This approach has already resulted in US FDA approval for *Vitrakvi* (larotrectinib), which got the green light in November for the treatment of both adults and children with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion; examples of tumor types with an NTRK fusion that have been shown to respond to the **Bayer AG**-partnered drug, a tropomyosin receptor kinase inhibitor, include soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer and lung cancer.

The Stamford, Connecticut-headquartered biotech, which was founded in 2013, is much more than a one-trick pony, however. Its second product, LOXO-292, is being developed for the treatment of patients with cancers that harbor abnormalities in the rearranged during transfection (RET) kinase. The first-in-class oral RET inhibitor, which is wholly owned, has been granted breakthrough therapy designation by the FDA for three indications – RET fusion positive non-small cell lung cancer, RET fusion positive thyroid cancer and RET mutant medullary thyroid cancer – with a potential launch in 2020.

Hold on tight: biopharma M&A merry-go-round is spinning again

"These molecules are great molecules – clean, on-target molecules that translate into a very positive profile," Lilly chief scientific officer Daniel Skovronsky told *Scrip* in an interview at the J.P. Morgan meeting on Jan. 7. "You have a hypothesis about which patients to target, you target it in those patients and they had extremely dramatic responses. This is exactly how drug development is supposed to work."

Skovronsky credited Loxo's co-founders – CEO Joshua Bilenker and COO Jacob Van Naarden – for seeing that "oncology would change to a point where we would be genetically profiling tumors and treating to the mutations or fusions that were present. They were willing to bet on that and then follow clear biology with great molecules given to the right patients."

"The challenge and the opportunity for us is to make sure we have a way of identifying the right patients in the clinic through diagnostics and making sure they get those medicines," he continued, "but both of them are first-in-class opportunities as well as best-in-class with dramatic responses for patients."

Further down the line is LOXO-305, an oral Bruton's tyrosine kinase (BTK) inhibitor, which is in Phase I/II trials and is designed to address acquired resistance to currently available BTK inhibitors, the most notable example being **AbbVie Inc.**'s blood cancer blockbuster *Imbruvica* (ibrutinib). Also in the pipeline is LOXO-195, a follow-on TRK inhibitor being studied by the company and Bayer for acquired resistance to Vitrakvi, which could be launched in 2022.

On a conference call, Lilly CEO Dave Ricks said the addition of Loxo would bolster the firm's oncology franchise and was consistent with its strategy of upgrading the pipeline as the company faces up to the effects of patent expiries on its lung cancer chemotherapy *Alimta* (pemetrexed). He also noted that last year Lilly acquired **Armo BioSciences Inc.** – and its immuno-oncology asset pegilodecakin – for $1.6bn. *(Also see "$1.6bn ARMO Buy Gives Lilly Its Most Advanced Immuno-Oncology Asset" - Scrip, 10 May, 2018.)*

Skovronsky told *Scrip* that the Loxo acquisition is "very different from the Armo deal. That was intentional. I think if you look at the Armo deal, what we are doing there – and we are still really excited about that one – is making a bet on biology. There the risk is, will it work? There's some data that suggests it will – we've talked in the past about monotherapy efficacy and some of the biomarker signals, but there's still a lot of uncertainty. If it works, it's a huge opportunity."

"This [Loxo deal] is a very different profile," he continued. "These molecules clearly work. If there is risk here, it's how much value we can create finding the right patients and commercializing them."

Much of the focus during Lilly's conference call was on LOXO-292, which Skovronsky told investors could be both first and best in class because of impressive overall response rates to date in the three aforementioned indications, and because

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of its good safety profile. Data from clinical trials so far indicate a 68% overall response rate in lung cancer and between 59% and 78% in thyroid cancer. The drug was described by Lilly as "the most substantial single component of the deal," and Skovronsky noted that between 94% and 100% of patients enrolled to date in the different indications are still in trials.

However, the future success of Vitrakvi and LOXO-292 will come down to testing and actually identifying the patients who have the fusions that the drugs treat. At present next-generation sequence (NGS) testing is limited and largely conducted only at major medical centers. Loxo's management has previously talked about the testing challenge.

Loxo formed a partnership in April with **Illumina Inc.** to develop a companion diagnostic that will use sequencing to identify whether patients' tumors carry a broad range of genomic signatures, while Bayer has been involved in discussions with several companies to produce a specific Vitrakvi test.

Discussing testing and LOXO-292 on the call, Lilly acknowledged the challenge, but pointed to increased tumor testing, particularly in lung cancer; the use of diagnostics in thyroid cancer is more limited at present. The company did not give any specific details about how it would tackle the testing problem, but Anne White, president of Lilly Oncology, did refer to her team's expertise in diagnostics.

Speaking about the Bayer partnership, she added that the company would be discussing the plans with the German group, but stressed that Lilly had a history of working "very successfully" on co-development and co-promotion alliances with big players, including its diabetes alliance with **Boehringer Ingelheim GMBH**. White, who noted that the deal highlighted the firm's focus on genetically defined cancers, is also hopeful that Loxo management and researchers will stay on board, stating that "what they've done in just five years is quite remarkable."

CEO Ricks noted that the proposed acquisition of Loxo did not preclude any other deals, saying that while the price tag was higher than Lilly had previously projected for purchases, it was getting four medicines in one package. He added that other oncology deals were possible, as it is an area where there are more options for acquisitions as the science continues to change apace, although Lilly's other specialized areas, notably immunology and diabetes, would still be very much of interest on the deals front. Ricks added that "it isn't out of range" to do a similar sized deal in the near future.

Skovronsky said he sees the Loxo transaction and last year's Armo acquisition as "very complementary and we want to do both kinds of deals as a company – those things that represent a high biology risk, but are potential game-changers, and then those that have a different risk profile. It's great to be in a company that can afford to have different types of uncorrelated risks – one in immuno-oncology and one in precision medicine."

"Those are the two pillars of our oncology strategy; we've said we're going to look at IO and we're going to look at tumor dependencies, and in the last year you've seen us do significant deals in both areas," he continued. "And there's more to come in both areas, both internally and through business development, but we intend to be leaders in those areas. I think this deal does now position us as a leader in precision medicine."

Initial response to the deal from analysts was positive. Alex Arfaei at BMO Capital Markets issued a note saying that "while we believe the proposed Loxo acquisition is expensive, we recognize that it is in-line with management's strategic focus on oncology and increased contribution from external innovation. Moreover, Lilly needs to optimize commercial scale for its oncology business."

He added that Loxo's targeted approach "is clearly part of the growing trend in cancer treatment," while pointing out that "the biggest risk is that the revenue potential is highly dependent on identification of a small subset of patients, competitive dynamics and the market's continued acceptance of the high prices." Loxo and Bayer set the wholesale acquisition cost of Vitrakvi at $32,800 for a 30-day supply of 100 mg capsules for adults, but introduced a money-back guarantee if patients do not respond within 90 days.

Andrew Berens at Leerink said that following the proposed BMS/Celgene link-up and **GlaxoSmithKline PLC**'s plans to buy **Tesaro Inc.** in a deal unveiled in December, he saw the Loxo buy "as validating significant value and interest in the targeted oncology space." He expects other early commercial and late-stage companies to benefit, notably **Blueprint Medicines Corp.**, "which has similar late-stage precision oncology assets, as well as a proprietary library of kinase inhibitors and drug discovery engine."

Unsurprisingly, Loxo shares soared after the deal was announced, leaping 66% to close at $232.65, while Lilly's stock edged up 0.6% to $115.28.

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Takeda's Weber: 'Everything Relies On Our Ability To Deliver Innovative Medicines'

IAN HAYDOCK ian.haydock@informa.com

A day before current **Shire PLC** employees globally get their new takeda.com email addresses, the acquisition's most public champion Christophe Weber said he is "excited and confident" about the combined company's future and **Takeda Pharmaceutical Co. Ltd.**'s transformation into what he sees as "a global, values-based, R&D-driven biopharmaceutical leader." The Japanese firm's president and CEO told a Tokyo press conference on Jan. 7 that innovation and focus would be the merged entity's best response to a global pharma operating environment marked by rising price pressures in many major markets, and that the im-

mediate priorities would be "a great and rapid integration" and getting the pipeline to patients globally as quickly as possible.

After months of pre-closing preparations, working through the procedures and logistics, and facing some hostility from influential shareholders in Japan, the CEO seemed to have retained a clear focus on the single most important priority of the deal: "Everything relies on our ability to deliver innovative medicines."

CREATING VALUE

With the challenges of shareholder approval now behind him, Frenchman Weber again stressed during the briefing at the Japanese firm's Tokyo headquarters that the $61bn equity value transaction – recently eclipsed in value terms by **Bristol-Myers Squibb Co.**'s planned $74bn acquisition of **Celgene Corp.** – would create a Takeda better able to deliver on multiple business and R&D fronts.

The compelling and "very strong" financial metrics, included envisioned pre-tax, run-rate synergies of at least $1.4bn annually by the end of fiscal 2021, maintained dividends, and significant underlying earnings per share accretion, would help the new Takeda better manage a more difficult environment.

"We have no doubt and are very confident in the medium term that we will have a top-tier margin, of 37% of EBITDA [earnings before interest, tax, depreciation and amortization] after synergies," the CEO declared.

This cash flow in turn will help the company pay back the net debt associated with the deal more quickly (to 2x adjusted EBITDA within three to five years) and invest in R&D, while in the meantime it is "very pleased" with the debt financing plans, which Weber and chief financial officer Costas Saroukos noted gave a "highly competitive" blended interest rate for Takeda's total debt of around 2.3%.

The company is due to issue its first major financial guidance post-completion in May, at the time of Takeda's results for the fiscal year ended March 31.

Touching on whether the planned BMS/Celgene deal could precipitate a further global consolidation this year, Weber told *Scrip* that: "We should step back and look at the global horizon. M&A has always been an important part of the global industry, with many of today's top global companies formed through such deals.

"We are an industry that invests highly in R&D 'at risk' and faces patent cliffs every so often, so it is natural that this is a response. It is getting very hard to find good opportunities that fit with strategy, but generally this [consolidation] is a trend that has been existing for years." While he said there would be some Takeda divestments "for sure in 2019," the executive gave nothing away on the likely post-completion shape of these, which he noted would take place to hone strategic focus and help pay down debt. But "we will look at non-core assets or where other companies could do a better job [with the asset] or we do not have critical mass."

The Japan consumer business has been mooted by some as a candidate, but Weber said that Takeda does have critical mass in this sector, hinting that the shedding of other non-core businesses outside Japan is being looked at and is more likely.

Takeda has already provided an "illustrative case" of up to around $10bn post-tax in non-core divestments, and this will be a closely watched area once the new company starts its formal combined operations on Jan. 8.

Snapshot Of The 'New Takeda'

- $31.3bn in combined revenues (49% from US, 18% from Japan, 14% from emerging markets)
- $10.1bn in adjusted EBITDA
- 33% of employees in US (12% of employees in Japan, 39% in emerging markets)
- Present in 80 countries, 30 manufacturing sites
- 21 pipeline assets in Phase II/III clinical development

GLOBAL LEADERSHIP TEAM

As already announced, three existing Shire external directors will join Takeda's board, while Weber pointed to a highly diverse (both nationality and gender-wise) post-completion core executive team, on which 16 of the 20 members will be non-Japanese.

The top 200 leaders of the combined company have already been identified, a team that will hold its first joint leadership conference this week. The success of the deal will to a large extent "be all about people and teams", Weber said, and a key topic of discussion at the meeting will be "patient trust" and case studies as to how this can be achieved.

Key considerations in the integration including ensuring balance and a lack of bias towards either company, although the ratio of Takeda/ex-Shire people in local implementing teams will be dependent on the pre-integration balance and appropriate expertise in each area. The internal board directors of the "new Takeda" include Weber along with Masato Iwasaki, president of the Japan Pharma Business Unit, and R&D President Dr Andrew Plump.

Apparently assuaging some concerns in Japan about the level of globalization within the company, while global reach is seen as a core benefit of the deal, Iwasaki stressed that Takeda's continued business presence in Japan will continue to be "very important".

The company is now in a position to accelerate the transformation of its operations in this market, in particular by leveraging its strong primary care presence for Shire's rare disease portfolio (which includes therapies for hematology, lysosomal storage disorders, and hereditary angioedema), and providing physician education in this sector.

THERAPEUTIC, R&D FOCUS

Again reiterating the combined company's strategic focus on the five areas of oncology, gastrointestinal, neuroscience, rare diseases and plasma-derived therapies, Weber maintained that the post-close operation would have the scale, investment and human expertise to be competitive in these areas, which together will account for around 75% of business globally.

"Some areas will grow more than others and some are facing pressures, but we are confident," he said. GI now accounts for around 30% of combined sales and oncology for 11%, but helped by the late-stage pipeline, the aim is to become a "global top 10 oncology player" with particular strength in hematologic malignancies and a growing lung cancer presence. Shire will bolster the post-deal company's rare disease play, a sector set for low double-digit growth.

Overall, around 40% of the current combined pipeline is partnered, around half of the pipeline has orphan drug designation.

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J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room

JESSICA MERRILL jessica.merrill@informa.com

The drug industry's biggest business meeting of the year, the J.P. Morgan Healthcare Conference, kicked off with a bang Jan. 7, with deal news that set an animated tone for the four-day meeting.

On the opening day, **Eli Lilly & Co.** announced an $8bn acquisition of genetics-based cancer company **Loxo Oncology Inc.**. That announcement, coming just days after **Bristol-Myers Squibb Co.** unveiled a $74bn merger with **Celgene Corp.** and weeks after **GlaxoSmithKline PLC** moved on **Tesaro Inc.** for $5.1bn, triggered a feeling of optimism that 2019 will be a big year for dealmaking – with plenty of speculation about what that will look like. *(Also see "Bristol/Celgene Made Perfect Sense, But Doesn't Promise Big M&A Year, EY Says" - Scrip, 8 Jan, 2019.)*

Other corporate updates trended positively, one of the biggest being **SAGE Therapeutics Inc.**'s positive Phase III data readout for an oral pill for post-partum depression, which could have even bigger commercial potential in major depressive disorder. *(Also see "Bristol/Celgene Made Perfect Sense, But Doesn't Promise Big M&A Year, EY Says" - Scrip, 8 Jan, 2019.)* The news sent the company's stock soaring 49% the day of the announcement, while Sage also awaits FDA approval of its first commercial drug, *Zulresso* (brexanolone), in March.

Most of the updates at J.P. Morgan were largely incremental, but maturing programs in highly innovative areas like gene therapy, cell therapy and RNA have drug makers and investors enthusiastic about the year ahead.

Nonetheless, growing public backlash over US drug pricing and gathering political headwinds, including a range of policy proposals aimed at curbing drug costs, cast a shadow over the whole affair. Industry tried its best to keep its head down and bask in the momentum, even as HHS Secretary Alex Azar launched a Twitter thread Jan. 9 berating industry over continued list price increases.

Drug makers did impose list price increases on their drugs in January, but generally those list price hikes were smaller than the double-digit price increases the industry used to rely on.

INNOVATION WORTH PAYING FOR

Those executives that were willing to address US drug pricing seemed to have landed on a collective message: innovation is worth paying for.

Regeneron Pharmaceuticals Inc. President George Yancopoulos argued passionately for industry to push back on some of the rhetoric and preserve innovation during the company's presentation in the Westin St. Francis.

"Yes, there are bad players. Yes, there are pricing problems. Yes, there are cost issues in all this, but we need innovation, and we have to protect it," he said. "Whatever solutions are put in place, there is nothing more important to our future as a society and as human beings than to continue supporting and, in fact, increase the incentives for innovation."

Novartis CEO Vas Narasimhan, to his credit, is stepping up as industry's leader on drug pricing, even as his company is getting ready to launch what could be the most expensive drug ever – the gene therapy AVXS-101 for spinal muscular atrophy.

He was one big pharma chief executive to take some ownership for industry's public perception problems in his presentation to investors in the grand ballroom, and he also participated in a Q&A on drug pricing held by J.P. Morgan.

"Yes, there are bad players. Yes, there are pricing problems. Yes, there are cost issues in all this, but we need innovation, and we have to protect it," Regeneron's President George Yancopoulos said.

"I'm very, very passionate about building trust with society," he said. "I believe our role as an industry over 100 years is incredibly important to society." But, "We've lost the trust of society by our behaviors." Smaller biopharmas were even less interested in reflecting on the macro environment. As **Sarepta Therapeutics Inc.** CEO Doug Ingram put it in an interview, "I am myopically focused. As an organization, we spend our time head down executing against our plans."

WHAT BLUEPRINT?

Last year at J.P. Morgan there was a lot of debate around rebate reform – and finger-pointing between pharma manufacturers and pharmacy benefit managers – but this year there was less policy debate, even as industry awaits word from HHS on rebate reform and a slew of other proposals that could represent a hit to pharma revenues have been announced. *(Also see "Rebate Reform: Big Changes Are Looming For The US Drug Market" - In Vivo, 12 Nov, 2018.)*

There was hardly even a mention of President Trump's drug pricing blueprint released in May. The consensus seemed to be to wait and see which proposals are actually going to move forward before beating any drums.

"I think companies are staying engaged. It's a top of mind head wind for them to think about, but they are not deterred from focusing on product roles, new pipelines," PwC's US Pharmaceutical and Life Sciences Leader Karen Young said in an interview.

Biogen Inc. CEO Michel Vounatsos, asked about HHS' proposed international pricing index for some Medicare Part B drugs, responded, "If it were to be passed there will be a reset for the entire industry … and the people that will win are the people who are able to innovate." Meanwhile, the government shutdown raged in Washington, D.C., keeping FDA Commissioner Scott Gottlieb from presenting his keynote address in person Jan. 8, but investors and drug

executives weren't especially fazed about potential fallout curbing development or regulatory timelines. That will change should the shutdown continue indefinitely and should FDA run out of carryover PDUFA fees to review drugs or meet with sponsors.

RESET AND REFOCUSED

Generally, there was a sense that industry has emerged from a reset in 2018, having digested the impact of US corporate tax reform, and in some cases new leadership and structures, prepared to execute on highly focused strategies.

GlaxoSmithKline PLC CEO Emma Walmsley and **Novartis AG**' Narasimhan are two new leaders with big ambitions to turn their big pharma engines into more nimble and innovative operations. Both have had time now to put their leadership teams in place and begin making cultural adjustments.

"It's that next layer of leadership that pushes a culture change through a very complex organization," GSK's Oncology Therapeutic Area Head Axel Hoos said in an interview about the changes underway at GSK. "I can feel it. It has arrived, at my level, and it is arriving now at other people's level. It trickles through the organization."

Pfizer Inc. also has a new CEO, Albert Bourla, who debuted in the Grand Ballroom Jan. 8 having just taken the reigns from Ian Read Jan. 1, while **Gilead Sciences Inc.**'s new CEO Daniel O'Day won't officially take over until March 1. It remains to be see how they will reshape their respective companies, but Bourla guided Pfizer investors to expect that he will continue to execute on the strategies put in place by Read.

"Things are changing in Pfizer now, but not because the leader is changing," he said. "In fact, thing are changing because the previous leader was successful."

GENE THERAPY: BUZZ, BUZZ, BUZZ

Gene therapy was the big buzz phrase around the streets of San Francisco over the course of the meeting, with everyone from investors to scientists to business development executives and commercial players all talking about the potential for one-time cures that could be on the horizon. Companies like Novartis, **Spark Therapeutics Inc.**, **Sarepta Therapeutics Inc.**, **bluebird bio Inc.** and **Voyager Therapeutics Inc.** have emerged as early leaders in the field and lots of others are hoping to stake a claim.

The neuroscience specialist **Denali Therapeutics Inc.** announced it is moving into gene therapy Jan. 9 through a partnership with **Sirion Biotech**, a developer of viral vector-based gene delivery technologies, to develop adeno-associated virus (AAV) vectors to get therapeutics to cross the blood-brain barrier, with the aim of developing a broad portfolio of product candidates for neurodegenerative disease.

Biogen Chief Medical Officer Alfred Sandrock reaffirmed the company's commitment to gene therapy in an interview. "We are aware of what is going on and we are looking at everything. It is likely that we will want to partner."

Gene therapy is going to be a big therapeutic area for deals, along with oncology, PwC's Young predicted.

"I think the key question is who are going to be the key players in that area, because it's not simple," she said. "I think they are all looking." But she added, "You have to know what you choose not to do as well and be able to articulate why aren't you going into that space."

Pricing for the expensive one-time gene therapies was a popular topic at J.P. Morgan. Bluebird CEO Nick Leschly laid out a plan to introduce a payment installment plan for its Lentiglobin gene therapy, which he said could be priced around $2m. It's the first time a drug company has detailed such a payment scheme. The drug is pending in Europe for beta-thalassemia and is on track for approval in the US in 2020.

Narasimhan also confirmed that Novartis is thinking about similar payment plans for AVXS-101. "I think we are prepared and planning on bringing out amortization models that would allow healthcare systems and payers to pay over time for these therapies based on the outcomes they deliver," he said. "The industry needs to put forth those models and then the payer systems need to adapt to be able to use those models, and that is a very different conversation."

With the building excitement around gene therapy and signs of progress tackling hard-to-treat rare diseases, cancer and neurodegenerative diseases, and with multi-billion dollar deals afoot after a lackluster 2018, industry was ready to accept a clap on the back at J.P. Morgan. But the reality is that the year could also deliver plenty of smacks.

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AstraZeneca Rejig Brings Baselga On Board

ALEX SHIMMINGS alex.shimmings@informa.com

Just days after news of the departures of Bahija Jallal and Mark Mallon from **AstraZeneca PLC**, the company has announced a reorganization at the top that will bring on board noted oncologist José Baselga, who recently resigned under a cloud as physician in chief at Memorial Sloan Kettering Cancer Center.

CEO Pascal Soriot said he was forming four new development and commercial units to align the company's R&D and commercial operations more closely in anticipation of "what we expect will be a period of sustained growth for years to come." The company returned to sales growth in the third quarter of 2018 and is expected to build on this in the coming year, based in large part on its oncology portfolio including PARP inhibitor *Lynparza* (olaparib), third-generation EGFR inhibitor *Tagrisso* (osimertinib) and checkpoint inhibitor *Imfinzi* (durvalumab).

The change in structure means that development of products will no longer be separated into early and late-stage but rather by development area. Specifically, AZ will create two therapy area-focused research and development units that will be responsible for discovery through to late-stage development: one for biopharmaceuticals (ie, its cardiovascular, renal & metabolism (CVRM) and respiratory areas), and another for oncology.

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Heading up the BioPharmaceuticals R&D unit will be Mene Pangalos, who was previously responsible for AZ's Innovative Medicines and Early Development Biotech Unit, and who has been credited with turning around R&D productivity at the firm. Baselga, meanwhile, will lead the Oncology R&D unit.

These two R&D units will be "mirrored" by two commercial units for BioPharmaceuticals and Oncology. "The creation of the BioPharmaceuticals commercial unit aligns product strategy and commercial delivery across CVRM and Respiratory," the company said.

José Baselga

Ruud Dobber will take charge of this BioPharmaceuticals commercial unit; he was most recently responsible for commercial operations in North America. This will be a twin of the company's existing commercial unit for Oncology, which will continue to be led by Dave Fredrickson. The International commercial organization, meanwhile, will remain under its current leadership.

The rejig is timely following last week's announcement that Bahija Jallal, the head of AZ's MedImmune LLC subsidiary, was leaving after more than 12 years to take on the role of CEO at **Immunocore Ltd.**, and that executive VP of global product and portfolio strategy Mark Mallon would leave the company after 24 years to become CEO of **Ironwood**. *(Also see "Jallal To Lead Immunocore, Building On Partnership She Forged At MedImmune" - Scrip, 4 Jan, 2019.)*

Soriot said the new structure would support his growth plans and "sharpen the focus on our main therapy areas," and he welcomed Baselga to the company, noting that his research and clinical achievements had led to the development of several innovative medicines.

Last September, Baselga resigned as physician-in-chief at Memorial Sloan Kettering Cancer Center following a controversy over his failure to disclose financial ties with healthcare firms in some of his research articles. He also stepped down from the board of **Bristol-Myers Squibb** at the same time.

AstraZeneca said this episode had little bearing on his new role."Dr. Baselga accepted that he had failed to make appropriate disclosures in a number of articles. Although the validity of the research was not in question, Dr Baselga has since updated the disclosures in those papers," it said in a statement to *Scrip*. "We are tremendously proud that he is adding to AstraZeneca's already exceptional expertise and that he will help us to continue building a world-class R&D unit for Oncology."

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Sage Impresses With Second Postpartum Depression Therapy

JOHN DAVIS john.davis@informa.com

The value of Cambridge, Mass.-based **SAGE Therapeutics Inc.**'s shares surged by 50% on Jan. 7 as the CNS-focused biotech released positive top-line Phase III results for its second lead compound, the orally administered SAGE-217, in postpartum depression, and the company's management presented an update of its commercial strategy at the J. P. Morgan Healthcare conference.

As well as the positive data, analysts attributed some of the excitement surrounding the company to it being a potential takeout candidate in the currently active M&A space. The new data also showed no loss-of-consciousness events so far with SAGE-217, a potential concern with the company's lead intravenously administered investigational compound, *Zulresso* (brexanolone), which may have overhung the stock, according to Leerink analysts.

SAGE-217 has previously shown strong data in major depressive disorder, and the current interim data show the drug has a rapid onset of action and produces durable responses, the Leerink analysts said in a Jan. 7 note. There are indications that SAGE-217 has blockbuster potential and could change the way depression is treated, although it will have to compete in a therapeutic sector that is highly genericized.

Biomedtracker analysts have been similarly upbeat, saying SAGE-217's novel mechanism of action, large treatment effect and indication selection may enable Sage Therapeutics to avoid the common pitfalls of antidepressant drug development.

Sage executives believe SAGE-217 should complement Zulresso, because patients react differently to various drugs, noted analysts at BMO Capital Markets. Sage Therapeutics is hoping to have some better-sleeping data in the label, and are considering additional clinical studies involving longer-term maintenance therapy, and switching from other antidepressants. SAGE-217 may also have a significant commercial opportunity in major depressive disorder, the analysts add.

SHORT-COURSE STUDY

In the Phase III ROBIN study, the efficacy and safety of a short course of SAGE-217 is being evaluated in 151 adult women with severe postpartum depression, and Hamilton Rating Scale for Depression (HAMD-17) scores of greater than 26.

Patients treated with SAGE-217 had a statistically significant improvement of 17.8 points in the Hamilton Rating Scale for Depression (HAMD-17) score, compared with 13.6 for placebo (primary endpoint, p=0.0029), after two weeks of outpatient therapy, Sage

Therapeutics reported on Jan. 7. Statistically significant differences between the two arms of the study were seen after three days and were maintained at each time point through the two weeks. The statistically significant reductions in HAMD-17 also continued through to the end of four weeks of follow-up, the company added.

45% of patients treated with SAGE-217 for two weeks achieved disease remission as measured by the HAMD-17, compared with 23% of patients receiving placebo (p=0.0122). Results from secondary endpoints were statistically significant and consistent with the primary endpoint, the company said.

SAGE-217 was generally well-tolerated with a safety profile consistent with that seen in earlier studies. Overall reports of adverse events were similar between SAGE-217 (58%) and placebo (51%) and included somnolence (12.8% with SAGE-217 versus 8.2% with placebo), headache (9% vs 12.3%), dizziness (7.7% vs 5.5%) and upper respiratory tract infection (7.7% vs 1.4%).

Two subjects experienced serious adverse events, one subject in each group. There were no reports of loss of consciousness or syncope, and no signal for increased suicidal ideation or suicidal behavior compared to baseline.

Postpartum depression is believed to be a distinct major depressive disorder that affects around one in nine women who give birth in the US, that is around 400,000 women annually, and is associated with functional impairment, depressed mood, lack of sleep and other symptoms.

Sage says SAGE-217 is a next-generation positive allosteric modulator that acts at synaptic and extra-synaptic GABA-A receptors and is also being developed for major depressive disorder and other mood disorders. The compound has already attracted attention from big pharma, with **Shionogi & Co. Ltd.** entering into an agreement in mid-2018 to develop and commercialize SAGE-217 in Japan, Taiwan and South Korea, with a large upfront of $90m.

A second pivotal Phase III trial of SAGE-217, MOUNTAIN, in patients with major depressive disorder, started in December 2018. Sage Therapeutics's lead compound, Zulresso, is awaiting US FDA approval, also for use in postpartum depression, with a PDUFA date for its priority review extended by three months to March 19, 2019.

Launch of Zulresso, if approved, is projected for June 2019, following scheduling by the US Drug Enforcement Agency.

Also in development at Sage Therapeutics are SAGE-324, which has potential in essential tremor and epileptiform disorders and is in Phase I, and SAGE-718, a first-in-class NMDA receptor positive allosteric modulator, also in Phase I for cognition-related disorders.

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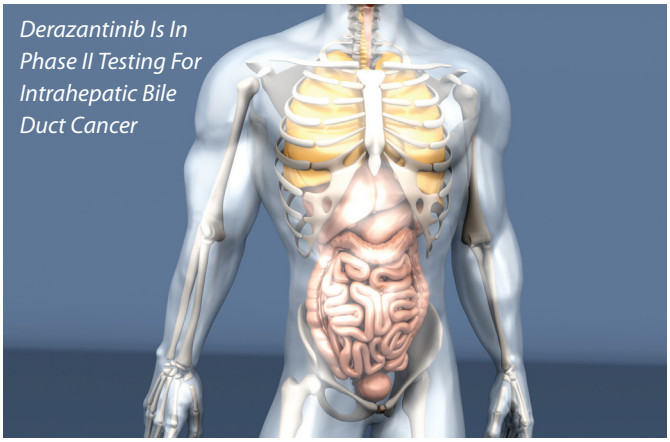
Basilea Says Phase II Derazantinib Data Keep Drug's Prospects On Track

STEN STOVALL sten.stovall@informa.com

Promising efficacy and safety tolerability shown by derazantinib in an interim analysis of its Phase II registrational study in bile duct cancer has reinforced **Basilea Pharmaceutica Ltd.** hopes of extending the clinical development program of the pan-fibroblast growth factor receptor inhibitor in other types of FGFR-driven solid tumors, the company said.

Derazantinib (BAL087, formerly ARQ 087) is a Phase III fibroblast growth factor receptor antagonist for intrahepatic cholangiocarcinoma (iCCA), a disease that starts in the bile ducts of the liver. Derazantinib has US and EU orphan drug designation for that disease.



Derazantinib Is In Phase II Testing For Intrahepatic Bile Duct Cancer

Basilea in-licensed derazantinib from **ArQule Inc.** in April 2018.

The drug candidate has demonstrated favorable clinical data in previous clinical studies, including a biomarker-driven Phase I/II study in iCCA patients. *(Also see "Deal Watch: Fresenius Drops Bid For Akorn, Citing Data-Integrity Concerns" - Scrip, 23 Apr, 2018.)* Under that in-licensing deal, Basilea received exclusive rights to develop and commercialize derazantinib worldwide, excluding China, Hong Kong, Macau and Taiwan. Earlier in 2018, ArQule Inc. granted **Roivant Sciences GMBH** and its **Sinovant Sciences Ltd.** division exclusive rights to develop, manufacture and sell the investigational cancer candidate in those Asian markets. *(Also see "Deal Watch: Roche Goes All-In On Real-World Data With Flatiron Acquisition" - Scrip, 19 Feb, 2018.)*

INTERIM PHASE II DATA DETAILS

Basilea on Jan. 9 said an interim analysis (which was conducted after 42 patients had been enrolled) of 29 evaluable patients who had at least one post-baseline imaging assessment showed an objective response rate (ORR) of 21%.

The disease control rate (DCR), reflecting the proportion of patients with a partial response or with stable disease, was 83%. The safety data obtained from all 42 patients enrolled at that point were consistent with the results from previous clinical studies with derazantinib.

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Marc Engelhardt, Basilea's chief medical officer, said in a statement: "The response rate and the safety profile at the time of the interim analysis are promising, especially considering the poor outcomes with chemotherapy in this group of patients reported in the literature. We are looking forward to the final data once the study is completed mid-2020."

The ongoing registrational open-label study is expected to enroll up to 100 patients with inoperable or advanced iCCA expressing FGFR2 gene fusions.

Under the trial, patients receive once-daily oral derazantinib to evaluate its anti-cancer activity with respect to objective response rate, progression free survival, overall survival and duration of response, and to further explore the safety and tolerability of the drug candidate.

SUPPORT EXTENSION PLANS

Engelhardt said the interim analysis of the trial had underscored the potential of derazantinib in the treatment of FGFR-driven tumors.

"We are planning to extend the clinical development program of derazantinib, by starting a Phase II study in other types of FGFR-driven solid tumors in mid-2019," he said. "We are also planning to expand the ongoing iCCA study by adding a separate cohort of patients with FGFR gene mutations to assess the potential expanded utility of derazantinib in the treatment of iCCA." Engelhardt added. The additional cohort of iCCA patients whose tumors express FGFR gene mutations is expected to enroll around 50 patients.

FGFR kinases are key drivers of cell proliferation, differentiation and migration. FGFR alterations, in the form of gene fusions, overexpression or mutations, have been identified as potentially important therapeutic targets for various cancers, including iCCA, bladder, breast, gastric and lung cancers.

Players in the field include US-based startup **QED Therapeutics**. It recently put its sole focus on the selective pan-fibroblast growth factor receptor (FGFR) inhibitor infigratinib which its parent **BridgeBio Pharma** licensed from **Novartis AG** and is advancing through its subsidiary after injecting $65m in seed money to develop the FGFR inhibitor. *(Also see "Start-up QED Touts Singular Focus On FGFR Inhibitor Infigratinib " - Scrip, 6 Jun, 2018.)*

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Mersana Axes Lead ADC Compound, Puts All Its Eggs In NaPi2b Basket

JO SHORTHOUSE joanne.shorthouse@informa.com

Antibody drug conjugate (ADC) biotech **Mersana Therapeutics Inc.** has thrown out its lead candidate XMT-1522. The ADC, partnered with **Takeda Pharmaceutical Co. Ltd.**, targeted HER2-expressing tumors and was built using Mersana's proprietary *Dolaflexin* platform.

Such was Takeda's early confidence in the ADC that it paid $40m up front in 2016 and agreed to pay another $20m once an IND was accepted by the FDA. Mersana retained all US and Canadian rights to the drug, with Takeda taking responsibility for rest-of-world commercialization. Mersana was responsible for all development up to Phase I, with Takeda planning to co-develop the drug on a 50/50 basis once Phase II began.

However, XMT-1522 had not been without its issues. A patient with a host of comorbidities had died while taking part in a dose-escalation Phase I clinical trial, leading to a partial clinical hold.

The company worked with the regulator in under 60 days to restart the trials in gastric, lung and breast cancer patients, and changed the dosing schedule of its two clinical programs, moving from a three- to four-week cycle based on early pharmacokinetic patient data.

> "Anna Protopapas, Mersana's CEO, said that XMT-1522 has been terminated, despite having a "favorable emerging profile of efficacy and tolerability", because of the "competitive environment for HER2-targeted therapies."

Anna Protopapas, Mersana's CEO, said that XMT-1522 has been terminated, despite having a "favorable emerging profile of efficacy and tolerability", because of the "competitive environment for HER2-targeted therapies."

Datamonitor Healthcare analyst Hardik Patel is of a similar opinion, telling *Scrip* that XMT-1522 "would not have had significant commercial potential for HER2+ diseases". The most obvious rivals come from **Roche**'s suite of HER2-targeted products, *Herceptin* (trastuzumab), *Perjeta* (pertuzumab) and direct competitor *Kadcyla* (ado-trastuzumab emtansine), an ADC approved since 2013 that has the benefit of physician familiarity.

There are also pipeline candidates that are much farther along in the clinic, such as **Daiichi Sankyo Co. Ltd.**'s DS-8201, a smart ADC chemotherapy composed of a humanized HER2 antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker. It is in Phase III trials for breast cancer, Phase II trials for colorectal cancer and NSCLC

and Phase I studies for solid tumors. And of course there is the biosimilar threat. The large number of Herceptin biosimilars now either approved or in late-phase development for HER2+ diseases means that patients and payers will have cheaper options available to them. "While these biosimilars versions of Herceptin may not have some of the benefits of HER2-targeted ADCs, trastuzumab has been considered the gold standard of treatment for HER2+ patients for almost two decades, and that is not likely to change anytime soon," Patel told *Scrip*.

"HIGHLY ENCOURAGING"

Analysts from Wedbush described the move as disappointing but "not entirely surprising," and seemed pretty happy about the Boston biotech pushing its unpartnered NaPi2b-targeting ADC, XMT-1536, to the fore as its lead candidate, stating that it had already become its "primary value driver" for the company.

In an October interview with *Scrip*, Eva Jack, Mersana's chief business officer, said the company was keen to partner up with another company to co-develop XMT-1536, and that it was "feeling really good about the program."

NaPi2b is a clinically validated ADC target broadly expressed in ovarian and non-small cell lung cancer (NSCLC).

Preliminary XMT-1536 data shows encouraging clinical activity at initial dose levels in heavily pretreated platinum resistant or refractory ovarian cancer patients. It showed a 25% objective response rate (ORR) in eight patients with platinum resistant/refractory ovarian cancer.

Analysts from Wedbush described this early clinical data as "highly encouraging" because it is comparable to mid-stage data in other ADCs studied in ovarian cancer, namely **Genentech Inc.**'s discontinued NaPi2b-targeted ADC lifastuzumab vedotin (LIFA) and **ImmunoGen Inc.**'s FolRα-targeted ADC mirvetuximab soravtansine.

Because Genentech chose to discontinue LIFA's development based on lack of durable benefit, Wedbush analysts said they would be looking for signs of durability as a "key determinant of the ADCs competitive position." Mersana is currently the only company pursuing NaPi2b as a target.

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Tizona Lands AbbVie Cancer R&D Deal As New CEO Takes Control

STEN STOVALL sten.stovall@informa.com

Privately-held biopharma **Tizona Therapeutics Inc.** got its New Year off to a good start by unveiling an early-stage cancer R&D collaboration with **AbbVie Inc.** by which the San Francisco-based biotech will receive a $105m upfront cash payment plus an equity injection from the big pharma.

News of the R&D pact - aimed at inhibiting the activity of CD39 - coincides with the arrival at Tizona of its new chief executive, Scott Clarke, formerly a high-ranking partnering executive at cancer specialist **Roche**, and comes soon after acceptance by the FDA of an IND application for Tizona's lead drug candidate, TTX-030, a first-in-class CD39-targeting immunotherapy.

PACT'S CD39 FOCUS

Under their collaboration, announced Jan. 4, AbbVie will have the exclusive option to license the CD39 program including TTX-030, after Tizona completes Phase Ib development. The biopharma has an option to co-develop and co-promote therapies in the US.

Tizona says its therapies are designed to 'modulate' the activity of immuno-suppressive cells by targeting the cell types and biological mechanisms responsible for immune suppression in the tumor microenvironment.

The ATP/adenosine axis has recently emerged as a key immune regulatory switch in the tumor microenvironment. Inhibition of CD39 with TTX-030 represents a novel and differentiated approach to targeting this pathway, Tizona and AbbVie said when announcing their collaboration.

Other companies investigating CD39-targeting immunotherapies include France's **Innate Pharma SA**, which recently entered a long-term immuno-oncology development partnership with **AstraZeneca PLC**. *(Also see "Innate Pharma's Expanded IO AstraZeneca Deal Jump-Starts US Ambitions" - Scrip, 23 Oct, 2018.)*

Founded in 2014, Tizona has additional preclinical product candidates targeting pro-inflammatory and anti-inflammatory signals that regulate the immune system's function.

HAILED BY NEW CEO

CEO Clarke joined the biotech on Jan. 1 from Roche where he served as global head of oncology partnering and head of Asia and emerging markets partnering.

"Tizona is poised to become a leading player in developing immunotherapies that target immune suppression, evasion and escape. I'm honored to join Tizona's high caliber leadership team in fulfilling this mission," Clarke said in a statement.

Its existing commercial collaborations include one with New Hampshire-based **Adimab LLC** to identify fully human antibodies against multiple targets selected and grants Tizona the right to develop and commercialize antibodies and bispecifics generated during their collaboration.

And under a collaboration entered in 2016 with **Ligand Pharmaceuticals Inc.**, Tizona is using the former's OmniAb transgenic animal platforms for producing mono- and bispecific human therapeutic antibodies.

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UroGen's Lead Product Data Back Barrett's Interest

JOHN DAVIS john.davis@informa.com

New York-based biotech **UroGen Pharma Ltd.** reported positive top-line Phase III clinical results with its lead compound, UGN-101 (mitomycin gel, 0.4%), in patients with low-grade upper tract urothelial cancer on Jan. 8, just under a week after the high-profile appointment of Liz Barrett as its president and CEO, and two days before a company presentation at the J.P. Morgan Healthcare Conference.

Upper tract (renal pelvis, ureter) urothelial carcinomas comprise about 5%-10% of all urothelial carcinomas, which can arise along any part of the urinary tract lined with urothelium. The majority of cases (90%–95%) occur in the lower tract (bladder, urethra).

The new data from the Phase III OLYMPUS study found that, on an intent-to-treat basis, 57% of 61 evaluable patients with low-grade upper tract urothelial cancer (LG UTUC) achieved a complete response at their primary disease evaluation timepoint (PDE, or the primary endpoint). This was conducted four to six weeks after completion of treatment, which consisted of instillation of UGN-101 once a week for six weeks through a standard ureteral catheter.

All evaluated patients with a complete response remained disease-free at six months, the company emphasized. A complete response was defined as a negative ureteroscopic evaluation and negative wash cytology, and around 45% of tumors were categorized as unresectable at baseline.

UGN-101 was delivered by instillation via the ureter, with administration achieved with UroGen's *RTGel* (reverse thermal gel) technology, which comprises a gel which is liquid at lower temperatures but becomes semi-solid at body temperature. The aim of the technology is to increase the time the urinary tract tissue is exposed to medication despite urine flow and tissue movement, making local therapy an effective treatment option, and reducing the need for repeated surgeries.

"The preliminary durability among evaluated patients was encouraging, considering radical kidney removal would be the only alternative," Jefferies analysts commented in a Jan. 8 note. They believe UGN-101 could be approved in 2019 and become a standard of care, in a market worth around $500m. Current therapy options include repetitive endoscopic surgical ablation, which is associated with high recurrence rates, or complete removal of a kidney, they note.

CONFIRMS INTERIM ANALYSIS

The new OLYMPUS data confirm the beneficial effects seen in an interim analysis conducted in May 2018, and UGN-101's progress towards becoming the first drug indicated for the non-surgical treatment of low grade UTUC is likely one of the reasons why Barrett, the former CEO of **Novartis AG**'s oncology business unit, Novartis Oncology, decided to lead the company , where her oncology drug commercialization experience will be invaluable.

UroGen reported in December 2018 that it had started a rolling submission of the NDA to the US FDA, with UGN-101 that has orphan drug, fast track and breakthrough therapy designations for the treatment of UTUC, and the company is preparing for potential commercialization of the product later in 2019.

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Monumental Year Ahead For Korean Pharmas As New US Approvals Eyed

JUNG WON SHIN jungwon.shin@informa.com

The South Korean pharma industry could be in for some pleasant surprises this year as several new pipeline drugs are slated to receive approvals from the US FDA or reveal their potential through key results from global Phase III trials. If the first revolution in the Korean pharma/biotech sector was major out-licensing deals, and the second was global biosimilar leadership, the third major stage will be the first launches of drugs with global potential, according to Kiwoom Securities.

"In the end, South Korea needs a global blockbuster drug. We may be able to witness this process in 2019," said the brokerage in a recent research report.

SK FIRST TO DEVELOP, LAUNCH, MARKET NEW DRUG IN US?

SK Biopharmaceuticals Co. Ltd. will be at the center of attention this year, as two of its new drug candidates are now undergoing the regulatory approval process in the US.

SK Group's new drug development arm, which focuses on developing novel CNS medicines, filed an NDA for its anti-epileptic drug cenobamate to the FDA in late 2018 and could receive an approval late this year.

Through its US subsidiary SK Life Science, SK Biopharmaceuticals is seeking to not only take the product through the regulatory process but also to market it independently, rather than seeking an out-licensing deal. If it successfully receives the approval, it will become the first Korean pharma firm to develop, launch and market an in-house developed new drug alone in a major global market. *(Also see "Committing To Drug Development In World's Biggest Market: SK's Story" - Scrip, 13 Mar, 2018.)*

SK Biopharmaceutical's sleep disorder drug candidate SKL-N05 (solriamfetol), which was licensed out to **Jazz Pharmaceuticals PLC**, is also undergoing regulatory review in the US, and the FDA's possible approval is expected in the first quarter.

HANMI'S POZIOTINIB, ROLONTIS SET FOR US APPROVAL

Hanmi Pharmaceutical Co. Ltd. is another company that could see some major approvals in global markets this year, although this time for drugs licensed out to overseas partners.

Although poziotinib, which is licensed out to **Spectrum Pharmaceuticals Inc.**, did not get a Breakthrough Therapy Designation from the US FDA based on Phase II data in patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 20 mutations, Spectrum said its overall development plan and timeline for an NDA filing based on the first cohort of the ZENITH20 trial remains unchanged.

The open-label, single-arm, multicenter global Phase II study is evaluating more than 300 NSCLC patients with EGFR or HER2 exon 20 insertion mutations. *(Also see "Spectrum To Test Poziotinib's Potential As First Line Treatment Of Exon 20 Mutant NSCLC " - Scrip, 19 Sep, 2018.)*

In late 2018, Spectrum also submitted a BLA with the US FDA for *Rolontis* (eflapegrastim), which is also in-licensed from Hanmi. *(Also see "Spectrum Gears Up To File Rolontis, Stresses Patient Access " - Scrip, 2 Jul, 2018.)*

The application is supported by data from two identically designed Phase III clinical trials, ADVANCE and RECOVER, which evaluated the safety and efficacy of Rolontis in 643 early-stage breast cancer patients for the treatment of neutropenia due to myelosuppressive cytoxic chemotherapy.

PHASE III OUTCOMES FOR VIROMED, SILLAJEN

Late-stage pipelines at biotechs **ViroMed Co. Ltd.** and **SillaJen Inc.** will also be under the spotlight, as ViroMed is set to unveil the outcome of its US Phase III clinical trial for VM202 in painful diabetic peripheral neuropathy (PDPN), and SillaJen is expected to disclose interim results from a global Phase III trial of *Pexa-Vec* for hepatocellular carcinoma.

VM202 is a proprietary gene therapy targeting four different indications - PDPN, peripheral arterial disease, coronary artery disease, and amyotrophic lateral sclerosis.

The first US Phase III clinical study in PDPN will end in the first half of 2019 and results are likely to be available in the latter half. As of June 21, 2018, 448 patients (94% of the planned total) had been randomized and 210 had completed the nine-month follow-up. The second US Phase III study, also in PDPN, is expected to be completed in 2020 or 2021. *(Also see "ViroMed's Plasmid DNA Facility Buy Addresses Key Potential US Regulatory Hurdle" - Scrip, 23 Jul, 2018.)*

How Korean biosimilars perform in the US market will also be closely watched this year

SillaJen is expected to complete global Phase III studies with Pexa-Vec, an oncolytic virus-based immunotherapy, for hepatocellular carcinoma, and to get results from a Phase Ib combination study being conducted with **Regeneron Pharmaceuticals Inc.**

Pexa-Vec (JX-594, pexastimogene devacirepvec) is the most advanced product candidate from the private South Korean biotherapeutics firm's proprietary SOLVE (Selective Oncolytic Vaccinia Engineering) platform. The therapy is based on the Wyeth strain of vaccinia virus and works through various mechanisms including direct cell lysis, adaptive immune response, and vascular shutdown. It is the first engineered oncolytic virus with demonstrated effective intravenous delivery to tumors.

GC Pharma, formerly known as Green Cross Corp., holds rights in South Korea, while **Lee's Pharmaceutical Holdings Ltd.** has licensed rights in China, Hong Kong and Macau, and **Transgene SA** in the EU, while SillaJen retains rights in all remaining territories.

ADDITIONAL LICENSING DEALS AFTER JPM?

The J.P Morgan Healthcare Conference last week was also being keenly monitored for additional licensing deals between Korean companies and global pharmas, which have picked up speed in general in recent months.

Yuanta Securities noted that Hanmi's triple agonist for obesity/non-alcoholic steatohepatitis (NASH) is poised to complete a Phase I trial in the first half of this year, making it one of the anticipated candidates for a out-licensing deal, given that it has the only weekly formulation among competitors from other company such as **Novo Nordisk AS** and **Sanofi**.

How Korean biosimilars perform in the US market will also be closely watched this year, amid increasing competition in this and other global markets, further evidenced by **AbbVie Inc.**'s decision to cut the price of original *Humira* (adalimumab). *(Also see "AbbVie Defends Humira With Aggressive Discount In First EU Tender " - Scrip, 1 Nov, 2018.)*

TAX INCENTIVES FOR OVERSEAS TRIALS

Regulatory wise, South Korea's drug ministry has vowed to continue its efforts this year to speed up the launch of innovative drugs and cutting edge medical devices, as well as to improve the predictability and transparency of the approval process.

The government plans to provide tax incentives related to the R&D cost of Phase III overseas clinical trials, while stepping up efforts to establish digital healthcare bases.

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Exscientia Bags Roche As AI Partner And $26m Series B To Fund Own Pipeline

STEN STOVALL sten.stovall@informa.com

Exscientia Ltd., the UK-based company that automates drug design with its AI-based platform, has added cancer specialist **Roche** to its growing list of pharma collaborators while also raising $26m in a Series B financing that will be used to aggressively expand its own pipeline in coming years.

Founded in 2012, Exscientia has been steadily expanding on the back of growing acceptance and use of artificial intelligence in drug innovation. A key driver in that pattern is the need to solve the problem of the escalating cost – and dwindling returns – of R&D.

Exscientia has now cashed in on that trend by successfully raising $26m in a Series B financing round announced on Jan. 7, money from which will be used to scale the company's pipeline and advance selected programs towards clinical development, its CEO told *Scrip*.

"This Series B marks a milestone in our development and enables us to drive the next phase of strong business growth," said Andrew Hopkins, CEO and founder of Exscientia.

He said the financing reflected investor enthusiasm that has been especially building over the past year amid expectations that Exscientia's first IND-ready programs, driven by AI, will come in the next 12 months.

"With this new funding, Exscientia is positioned to become the dominant player in AI drug discovery, driving radical change in R&D productivity," he predicted. The Series B round included participation from new investors **Celgene Corp.** and specialist healthcare investor **GT Healthcare Capital Partners**, as well as existing investor **Evotec AG**.

ROCHE COLLABORATION LAUNCHED

The financing round coincided with news of a drug discovery collaboration between Exscientia and Swiss drug giant Roche.

Exscientia will receive upfront and research funding as well as preclinical, development and commercial milestone payments collectively worth up to CHF67m ($68m), plus tiered royalties on the annual net sales of any products resulting from the collaboration. No further financial details were disclosed.

"We are working on a project of very high interest to Roche but we cannot disclose the target or therapeutic area at this stage," Hopkins said.

"This is really the first AI drug discovery deal that Roche has done so we are incredibly pleased that, out of all the companies Roche has spoken with, they chose us," Hopkins said, adding: "We are also pleased that the deal is very accretive to us and puts Exscientia in a very strong position revenue-wise."

The collaboration represents the sixth drug discover partnership for Exscientia and adds Roche to its list of big pharma partners that already includes **GlaxoSmithKline PLC**, **Sanofi** and Evotec. *(Also see "Evotec Invests €15m In AI-driven Exscientia" - Scrip, 28 Sep, 2017.)*

In 2018, Exscientia bought AI firm Kinetic Discovery, thereby bringing on board 'biophysics' capabilities to supplement its artificial intelligence-driven drug discovery and design capabilities and boosting Exscientia's headcount to around 35 employees.

CEO Hopkins said the company would now evolve as a self-generator of products.

"We now have the in-house capability to go from idea generation using a AI-platform to completion of IND projects."

Last year, the AI specialist developed around seven drug discovery programs, according to Exscientia's executive chairman Alex Snow.

Formerly CEO of the hedge fund Lansdowne Partners, Snow, who joined Exscientia in 2017, said the AI firm's platform now had the potential to bring a generation of new medicines to the market "by offering a technologically and financially superior approach to drug discovery that will benefit patients."

"By investing in our business, and building out our technology platform, we hope to take on something like 20 discovery programs in 2019. In 2020 and the following years we would hopefully be looking to deliver between 30 and 40 discovery programs per year," Snow told *Scrip*.

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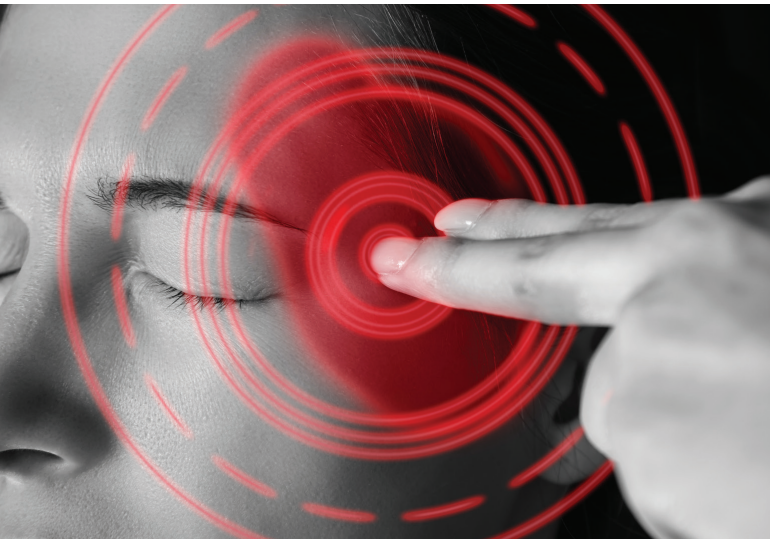
Novartis Gets NICE Headache From Aimovig Knockback

KEVIN GROGAN kevin.grogan@informa.com

Novartis AG and migraine patients in the UK have been left reeling by NICE rejecting *Aimovig* (erenumab) in draft guidance, deeming the first new drug for the condition in over 20 years to be too expensive for use on the NHS.

The cost-effectiveness watchdog looked at Aimovig for preventing chronic and episodic migraine in adults who have four episodes or more every month where at least three oral previous preventive treatments have failed. While acknowledging "the evidence shows that erenumab is a clinically effective treatment," NICE said trial data "doesn't fully reflect patients seen in clinical practice in the NHS … nor does it include all the relevant comparators and outcomes," and the cost-effectiveness estimates for the once-monthly, self-injection "are higher than what NICE usually considers to be acceptable when there is substantial uncertainty."



Aimovig, approved in Europe last July, costs around £5,000 per year at its list price, although a confidential commercial arrangement has been agreed with Novartis which would have made it available at a discounted price. In a statement, Meindert Boysen, director of the Centre for Health Technology Evaluation at NICE, said it had heard from patient experts that well-tolerated treatment options are needed and it is "disappointing that we've not been able to make a positive recommendation." *(Also see "ICER Says Amgen/Novartis Migraine Drug Aimovig Is Cost Effective At $5,000 Net Price" - Scrip, 1 Jun, 2018.)*

Current treatment options for preventing migraine include beta blockers, antidepressants and epilepsy medications which can have significant side effects and be ineffective for many patients. For those people with chronic migraine for whom at least three oral treatments have failed, NICE currently recommends **Allergan PLC**'s *Botox* (botulinum toxin type A) as an option and Boysen claimed there was not enough evidence to suggest that Aimovig, a calcitonin gene-related peptide (CGRP) inhibitor partnered with **Amgen Inc.**, was more effective than the latter nor are there data to show the Novartis drug is effective in the long term in those patients.

Boysen ended on a positive note, saying that "we will work with the company to ensure that they are given every opportunity to address the issues highlighted in these provisional recommendations."

Haseeb Ahmad, country president of Novartis UK, said in an email to *Scrip* that the company is disappointed "yet welcomes the opportunity to further discuss our submission." He added that the priority now was to continue working closely with NICE and quickly address any outstanding questions it has so that patients will not be denied access to the first licensed treatment specifically designed to prevent migraine.

However, Ahmad argued that "NICE does not consider the impact of diseases on broader society when evaluating the cost-effectiveness of medicines." He pointed out that "as migraine predominantly affects people of working age, it costs the UK economy £8.8bn per year in lost productivity alone," citing figures from the not-for-profit Work Foundation.

He also stressed the quality of life benefits, noting that unlike Botox, "Aimovig can be self-administered at home and does not require repeated clinic visits or multiple injections into the head and neck." Patients treated with Botox can require up to 40 injections by a specialist. The NICE knockback for Aimovig is the latest example of pharmaceutical companies being frustrated by the agency in their attempts to get to market quickly after approval. According to Office for Life Sciences data, the UK already lags significantly behind other European countries in the ability for patients to access new medicines and on average, the uptake of NICE-approved medicines in the first year after launch in the UK is worse than in comparator countries including France and Germany.

Aimovig is expected to be a key growth driver for Novartis, which told *Scrip* that the drug is reimbursed in Sweden and is currently under consideration in other regions. The market in the UK is a big one and NICE estimates that there are 190,000 migraine attacks experienced every day in England with women more likely to experience one than men (5-25% versus 2-10% respectively).

However, unless the decision is reversed, the only option for sufferers is to go private. Wendy Thomas, chief executive of the Migraine Trust, described NICE's move in a statement sent to *Scrip* as "extremely disappointing, and devastating for people whose lives are blighted by migraine." She added that "it is terrible that people with migraine have had to wait so long for their own treatment… now, after proving effective to many, it is not accessible to those who can't afford to purchase it privately." On a private basis, treatment with Aimovig costs around £380 a month.

The National Migraine Centre is the only charity in the UK that diagnoses and treats people with the condition and is prescribing Aimovig. One of its headache specialist doctors, Katy Munro, told *Scrip* that "the feedback has been positive about the effectiveness and the ease of use. We feel this may be a very promising new treatment for migraine sufferers and are disappointed that it will not be more easily available. We hope the issues raised by NICE can be addressed so that this innovative treatment can be offered."

Charlotte Burr, operations director at the National Migraine Centre, added that "demand has already been quite high for this

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new drug and we have had a lot of interest from all over the UK and even calls from across the world asking if they could come to us to acquire Aimovig." She told *Scrip* that "we haven't been prescribing this for very long, but currently have over 30 patients using Aimovig and we expect this number to rise rapidly as more people find out about this new treatment."

David Bloomfield, the center's chief executive, added that some of its patients had already benefited from treatment "and we know that many sufferers are waiting anxiously for Aimovig to be made available on the NHS. We hope that NICE and Novartis are able to resolve the current impasse and clinicians are provided with another treatment option."

Watching very closely how the negotiations go between NICE and Novartis will be the other players in the CGRP inhibitor field class. **Eli Lilly & Co.** won EU approval for *Emgality* (galcanezumab) in November, while **Teva Pharmaceutical Industries Ltd.** is hoping to hear soon from the European Medicines Agency about fremanezumab, which was accepted for review on this side of the Atlantic in February 2018 and approved in the US as *Ajovy* in September last year. Further back, **Alder Biopharmaceuticals Inc.** is expected to file a marketing application in Europe for eptinezumab this year. *(Also see "Lilly Moves Into Migraine Race With CHMP Okay" - Scrip, 24 Sep, 2018.)*

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Lundbeck Launches Rexulti In Europe, Phase II LU AF11167 Trial In Schizophrenia

STEN STOVALL sten.stovall@informa.com

Denmark-based **H. Lundbeck AS** has initiated a Phase II schizophrenia trial for its candidate drug Lu AF11167 that inhibits the PDE10 enzyme in the brain and which the CNS innovator believes could be a novel approach to manage the difficult-to-treat negative symptoms associated with schizophrenia.

The trial's start coincided with Lundbeck's launch in Switzerland of *Rexulti* (brexpiprazole) for treating adult patients with schizophrenia, the first in a sequence of roll-outs that will see the treatment made available in other European countries during 2019 and 2020.

REXULTI ENTERS EUROPE

"We hope the reception for Rexulti will be good in Europe. It has been very well received by patients and doctors in the markets where it's available so we certainly hope and expect that it will get the same reception in the EU," Mads Dalsgaard, who heads clinical development at Lundbeck, told *Scrip*.

Rexulti is already on the market in the US, Australia, Canada, Saudi Arabia, and Japan as a treatment for schizophrenia in adults. The compound was discovered by **Otsuka Holdings Co. Ltd.** and is being co-developed by **Otsuka Pharmaceutical Co. Ltd.** and Lundbeck.

Dalsgaard confirmed in an interview that Lundbeck will soon be announcing top-line results from two Phase II trials studying Rexulti in bipolar disorder.

The mechanism of action for Rexulti is not fully understood, but the compound's efficacy may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors.

AMID WIDER CONCERNS

While Lundbeck's hopes are high for the drug's European prospects as a treatment for schizophrenia, analysts at Bernstein are more cautious, saying in a recent note that "we do not expect Europe to be a sizable region for Rexulti, and estimate sales in the area at around €180m."

Lundbeck, which is facing generic erosion of revenues from its key drugs, is hoping for fresh sources of revenue. *(Also see "Generic Blow Looms For Lundbeck" - Scrip, 8 Aug, 2018.)*

Concerns about where that may come from were heightened last October with the failure of the Phase III DAYBREAK trial of antipsychotic AF35700. *(Also see "The Darkest Hour Is After DAYBREAK For Lundbeck's New Antipsychotic " - Scrip, 26 Oct, 2018.)* That upset was the latest in a string of Phase III trial disappointments, including the mixed findings for Rexulti in agitation in Alzheimer's disease (AD) dementia necessitating a third trial, and the all-out failure of idalopirdine in AD.

> "It has been very well received by patients and doctors in the markets where it's available so we certainly hope and expect that it will get the same reception in the EU." senior vice president, clinical development, Lundbeck.

AS LU AF11167 ENTERS PHASE II

Dalsgaard said the primary objective of the just launched Phase II evaluation of Lu AF11167 is to evaluate the efficacy on negative symptoms of two doses of the compound versus placebo as monotherapy in patients with schizophrenia and persistent prominent negative symptoms.

Lu AF11167 inhibits a phosphodiesterase enzyme, the PDE10 mainly found in the brain and areas linked to neurological and psychiatric illnesses in patients.

"The PDE10 inhibits an enzyme that is present or expressed within the same signalling pathways where a normal antipsychotic works, but it modulates that signalling – the dopamine sig-

nalling – in a different way and one that is believed to positively influence the negative symptoms as well as support cognition," Dalsgaard explained.

The secondary objective will be to evaluate the efficacy of Lu AF11167 on patients' functioning as well as the safety and tolerability of the compound. The three-arm study will randomize a total of 240 patients with 80 patients per arm from various European countries.

"Participants are relatively clinically stable schizophrenia patients who have been on a stable dose of their antipsychotic medication and they are regarded as outpatients but they have a prominent degree of negative symptoms," Dalsgaard explained, adding: "We hope to have data from the study by the summer of 2020 and if it produces positive results we would take it to Phase III."

Jefferies analyst Peter Welford said in a recent note that "We currently ascribe no value to '11167 in our valuation, however, positive Phase II data supporting further development could be worth around DKK20 to Lundbeck's share value."

Meanwhile Lundbeck is still trying to assess what to do with Lu AF35700. Decisions are likely to follow the imminent readout of the Phase III Anew trial in patients with early-in-disease (ED) or late-in-disease (LD) treatment-resistant schizophrenia.

Lundbeck's new CEO Deborah Dunsire launched a strategic review upon her arrival in September, with an outcome expected with the 2018 results in February.

If Lu AF35700 is eventually abandoned then Lundbeck's pipeline of new compounds would be headed by glutamate receptor modulator foliglurax, which is in Phase II for Parkinson's disease, followed by various projects in Phase I, including amyloid-targeting Lu AF20513 for Alzheimer's disease. *(Also see "Lundbeck Breaks Into MAb Development, Adds To Suite Of Parkinson's Candidates" - Scrip, 7 Aug, 2018.)* Jefferies' Welford commented: "Whilst management has stated that the initial priority will be the internal pipeline, we believe investors will likely welcome business development deals, given the paucity of late-stage pipeline assets."

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Pfizer Pulls Plug On Two Unviable Indian Sites, Over 1,500 Jobs At Risk

ANJU GHANGURDE anju.ghangurde@informa.com

Over 1,000 jobs could be at risk in India after **Pfizer Inc.** said that it was ending production activity at two "unviable" facilities, including the troubled Irungattukottai (IKKT) plant in Tamil Nadu.

Both facilities – the IKKT plant and the other in Aurangabad – came to Pfizer via the acquisition of **Hospira Inc.** in 2015 and will immediately cease manufacturing. Pfizer expects to exit the sites "as soon as possible in 2019".

The US multinational said that it had decided to end production at the locations after a thorough evaluation, which concluded that due to the "very significant long-term loss of product demand" manufacturing at the plants is not viable.

The IKKT facility has also been under regulatory fire over the past few years. Last year, Pfizer paused production at the facility to remediate compliance issues flagged by the US FDA.

IKKT has around 1,000 employees, while the Aurangabad site has approximately 700 personnel. Pfizer said that it is committed to keeping colleagues impacted by the decision "informed of the site exit process".

Both sites fall under the ambit of Pfizer Healthcare India Private Limited, a subsidiary of Pfizer Inc, US and not the listed Indian arm **Pfizer Ltd.**

NO CURRENT ONGOING MANUFACTURING TRANSFERS

The IKKT site, which Hospira inherited as part of its 2009 acquisition of **Orchid Chemicals & Pharmaceuticals Ltd.**'s injectables business, was said to manufacture generic injectable cephalosporins, penems and penicillin, while the Aurangabad facility supported the IKKT plant with the supply of penems and penicillin.

Pfizer, however, clarified to *Scrip* that there are "no current ongoing manufacturing transfers" of these products to other sites. "Most of these products will be discontinued now due to the very significant long-term loss of product demand," it said.

No India supply issues are envisaged either. Both the IKKT and Aurangabad sites were purely export-oriented and did not supply products for Pfizer's India commercial operations.

"This announcement does not affect our other Indian manufacturing sites in Goa, Vishakapatnam (Vizag) and our joint venture site, ZHOPL [Zydus Hospira Oncology Pvt Ltd; a JV with the India's **Zydus Cadila** group], in Ahmedabad," Pfizer stressed.

VIZAG SITE REPURPOSED

Pfizer also sought to allay any concerns around whether it was planning a widespread cut-back in Indian manufacturing. The US multinational emphasized that it was, in fact, set to expand operations at its Vizag site in India.

"The Vizag site is now being expanded into a global Terminally Sterilized Manufacturing Center of Excellence (TS COE). It will cater to export markets, such as the US and eventually we expect to Canada," Pfizer said, adding that India will continue to be an important manufacturing location for Pfizer worldwide.

The company explained to *Scrip* that, based on a comprehensive review of the company's global manufacturing network and the capacity of the Vizag plant, it had now decided to "repurpose" the facility into a TS COE.

"It acknowledges Vizag's demonstrated capabilities to deliver TS products. There are no plans to exit other manufacturing sites in India," Pfizer added.

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Standing On The Shoulders Of Giants: Could Arecor Enter The Race To Revolutionize Diabetes?

JO SHORTHOUSE joanne.shorthouse@informa.com

No longer just a **Unilever PLC** spin-out helping pharma reformulate drugs, **Arecor Ltd.** has now made the first moves to becoming a drug development company in its own right. With money in the bank from its latest fund raising, new institutional investors on board and a fresh Clinical Trial Application with the regulators, it may be Arecor's moment to come out from the technology partnering shadows and put itself in the spotlight. CEO Sarah Howell talks to *Scrip* about the company's plans for developing its own diabetes drugs.

To date, Arecor's business model has pivoted around its proprietary technology platform, Arestat, which reformulates products in development or already on the market and develops superior versions of those available. It works with the top 20 global pharma companies to improve the formulation and administration of drugs, enabling intravenous drugs to be dosed with a single injection, for example.

This technology, and the company's experience in reinventing existing products, makes it very well-qualified to enter the diabetes landscape, Howell told *Scrip*.

"Ultimately, there is a huge amount of unmet need in diabetes and it's a large market," she said. "There's a significant market opportunity for Arecor and our USP is that we can deliver improved products that are simply not possible without using our technology, that really enables us to play in an area such as diabetes which is dominated by major pharma."

That includes companies such as **Novo Nordisk AS** and **Eli Lilly & Co.**, both of which have fast-acting insulin products. French biotech **Adocia SAS** has also announced the first home-use trial to test its BioChaperone Lispro in an autonomous insulin delivery system, the iLet, an artificial pancreas delivery system.

Fueled by a £6m equity investment, led by UK institutional investors Calculus Capital, Downing Ventures, and Albion Capital, Arecor is putting its money where its mouth is and has filed a Clinical Trial Application to conduct a Phase I study in Type 1 diabetic patients at a clinical trial site in Austria. The study will compare the pharmacokinetic and pharmacodynamic profiles of its ultra-rapid acting insulin product, AT247, to that of Novo Nordisk products *NovoLog* (insulin aspart) and its fast-acting version, *Fiasp*.

Even with large pharma heavily investing in the field of rapid-acting insulin, Howell believes small companies have the impetus to create value. "There is a lot in development, but we believe there is a lot of room for further improvement. The aim is to have the fastest-acting insulin physically possible to market," she said.

Arecor hopes to be dosing patients by the end of the first quarter of this year, with a full readout in Q4. The product follows a 505b2 pathway, an abbreviated development and regulatory pathway because safety and efficacy is already known.

Arecor will do a series of Phase I studies to demonstrate different characteristics of the product but once these are complete the product will skip Phase II, moving straight to Phase III. At this stage, the company would like to bring on a partner to embark on late-stage development and commercialization.

Arecor CEO Sarah Howell

"There is a lot in development, but we believe there is a lot of room for further improvement. The aim is to have the fastest-acting insulin physically possible to market"

Howell recognizes that with 425 million diabetics worldwide generating annual insulin sales of $22bn, a significant sales and marketing effort is required to play in this therapeutic space. Arecor would look to partner with a company that already has that commercial arm in place, that has a need for rapid-acting insulins and that can capture the market share.

UNILEVER SPIN-OUT

Arecor was spun out from Unilever in 2007 as a protein stabilization company, initially for a wound dressing that was going to be used in the field, led by Jan Jezek, Arecor's existing CSO, and Paul Davies, whose other achievements include the invention of the Clear Blue pregnancy test. The early phases of the company focused heavily on technology development, but it was with the

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

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

PIPELINE WATCH, 4–10 JANUARY 2019

Event Type	Lead Company	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	UroGen Pharma, Ltd.	mitomycin C gel	Upper Tract Urothelial Cancer	OLYMPUS; Positive Results	0	82
Phase III Top-Line Results	Liquidia Technologies, Inc.	LIQ861 (treprostinil) inhalation	Pulmonary Arterial Hypertension	INSPIRE; Encouraging Results	2	49
Phase III Top-Line Results	Allergan plc	bimatoprost Sustained Release	Glaucoma/Ocular Hypertension	092; Postive Results	3	59
Phase III Top-Line Results	Bristol-Myers Squibb	Opdivo (nivolumab)	Esophageal Cancer	ATTRACTION-3; OS Extended	5	40
Phase III Top-Line Results	Sumitomo Dainippon Pharma Co.	Latuda (lurasidone)	Schizophrenia	JEWEL (EU, Japan); Met Primary Endpoint	0	100
Phase IIIa Top-Line Results	SAGE Therapeutics/Shionogi	SAGE-217	Post-Partum Depression	ROBIN (PPD-201); Met Primary Endpoint	2	61
Phase III Trial Initiation	MC2 Therapeutics A/S	MC2-01	Psoriasis	An EU Study	0	67
Phase III Trial Initiation	SAGE Therapeutics/Shionogi	SAGE-217	Major Depressive Disorder, Insomnia	SHORELINE, RAINFOREST; Pivotal Studies	0	61
Phase III Trial Initiation	Roche/Ionis	HTT-ASO	Huntington's Disease	BN40423; Trial Underway	35	54
Phase III Trial Initiation	Alnylam/Sanofi	vutrisiran	hATTR Amyloidosis With Polyneuropathy	HELIOS A; In 160 Patients	-	62
Phase III Trial Initiation	Aprea Therapeutics AB	APR-246	Myelodysplastic Syndrome	Frontline (w/Azacitidine); Actively Enrolling	25	35
Phase III Trial Initiation	Pacira Pharmaceuticals, Inc.	Exparel (bupivacaine) Inj.	Postsurgical Pain	PLAY (Pediatric); Protocol Agreed	0	100
Phase III Trial Announced	BioCryst Pharmaceuticals, Inc.	BCX7353	Hereditary Angioedema	Acute HAE Study; In Mid-2019	0	63
Phase III Trial Announced	Mirati Therapeutics	sitravatinib	Non-Small Cell Lung Cancer	vs. docetaxel; Second-Line	0	11
Phase III Trial Announced	Alnylam Pharmaceuticals, Inc.	Onpattro (patisiran)	hATTR Amyloidosis With Cardiomyopathy	APOLLO B; Double Blind Study	0	100

Source: Biomedtracker | Informa, 2019

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arrival of Howell as CEO in 2015 that the company began to have ambitions outside its revenue-making technology stream. Howell joined from UK biotech **BTG PLC**, before that working on product development at **UCB Group**, predominantly on rheumatoid arthritis drug *Cimzia*, and before that **GlaxoSmithKline PLC**.

Howell joined Arecor as CEO because she felt there was opportunity in its technology, but it needed to morph from a R&D organization to a development and commercialization outfit, and needed someone from a pharma background to accomplish this. "It's difficult to partner with pharma if you don't understand pharma," Howell explained. Howell could see that Arecor's technology business was valuable. Its pharma partners pay to create new formulations, and when they take them into development it is under a technology licensing model which makes it milestone and royalty bearing, with a significant value upside.

"We have proven over the years by working with pharma that we're able to deliver improved products that they simply are unable to deliver themselves, so why don't we move ourselves further up that value chain and take products through development ourselves?" she recalls asking when she took the reins three years ago. Arecor carved out diabetes as a therapeutic area of interest because it could take products forward by itself and move through development at speed.

Howell admits there are risks involved in this business strategy, but believes they are manageable. "It's a risk because we're spending money rather than just generating revenue, but that's mitigated by the fact that we're taking already approved pharmaceutical products and repurposing them. The biggest risk in pharmaceutical product development is around clinical efficacy and safety, whereas that risk for us is very low. Its already been proven but we're looking to further improve them. The biggest risk is around picking the right products and understanding what the patient needs, and what the commercial landscape is for this product."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Francesca Domenech Wuttke	Almirall SA	Chief Digital Officer and Management Board Member	Novartis AG	Global Director, Commercial Strategy	4-Jan-19
Angie You	Amunix Operating Inc	Chief Executive Officer	Sierra Oncology	Chief Business and Strategy Officer and Head, Commercial	3-Jan-19
Jamie Oliver	ChemioCare	Chief Medical Officer	Accelovance Inc	Chief Scientific Officer	7-Jan-19
Bryan E. Stuart	Fulcrum Therapeutics	Chief Operating Officer	Yarra Theraputics	Chief Executive Officer and President	3-Jan-19
Michael Shetzline	Ironwood Pharmaceuticals Inc	Chief Medical Officer, Senior Vice President and Head, Drug Development	Takeda Pharmaceuticals International Co	Vice President and Head, Gastroenterology Clinical Sciences	28-Jan-19
Amy Sullivan	Kiadis Pharma	Senior Vice President, Corporate affairs	Keryx Biopharmaceuticals	Senior Vice President, Corporate Affairs	4-Jan-19
Neil H. Shusterman	Palladio Biosciences	Chief Medical Officer	Endo Pharmaceuticals Inc	Chief Medical Officer	3-Jan-19
Clinton Musil	Personalis Inc	Chief Business Officer	ARMO Biosciences	Vice President, Corporate Development	3-Jan-19
Eduard Gorina	Pliant Therapeutics	Vice President, Clinical Development	FibroGen	Executive Director	3-Jan-19
Tony Kingsley	TARIS BioMedical LLC	Chief Executive Officer, President and Director	The Medicines Company	President and Chief Operating Officer	3-Jan-19
Scott Clarke	Tizona Therapeutics Inc	Chief Executive Officer	Roche	Global Head, Oncology Partnering and Head, Asia and Emerging Markets Partnering	3-Jan-19

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General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com