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Amid New M&A Rumors, Amarin CEO Focused On Vascepa Approval

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Novartis AG's $9.7bn move to acquire The Medicines Company and its first-in-class siRNA cholesterol lowering drug, inclisiran, has generated a new buzz around novel cardiovascular medicine companies and other M&A targets.

Unveiled on 24 November, the deal has set the rumor mill whirring on who might be next on big pharma's M&A wish list, and has lifted the share prices of several likely targets.

Chief among these is New Jersey-headquartered Amarin Corporation, which looks to be just days away from securing a US label expansion of its omega-3 fish oil based cardiovascular treatment Vascepa (icosapent ethyl).

Excitement has been building around Vascepa since Amarin unveiled some remarkable results a year ago from its REDUCE-IT cardiovascular outcomes trial.

This showed the twice-daily pill produced a 25% relative risk reduction in cardiovascular events in patients already taking statins and with established cardiovascular (CV) disease, diabetes or other CV risk factors.

It showed equally impressive results in secondary endpoints in CV death (20% rrr), heart attack (31%) and stroke (28%), results which far exceed any other add-on treatment in the market, including the PCKS9 inhibitors, Repatha and Praluent. *(Also see "New CV Outcomes Study May Mean Big Boost For Amgen's Repatha Market" - Scrip, 15 Mar, 2019.)*

The US Food and Drug Administration is due to announce its decision by 28 December or earlier following a unanimous recommendation from an FDA committee earlier this month.

Amarin will be hoping to negotiate a label which allows as broad an interpretation of its use as possible, which would involve use in primary and secondary prevention of a cardiovascular event.

If the company can secure this label, and execute well on its salesforce expansion and planned US direct-to-consumer advertising, analysts think the drug could hit $4bn in peak annual revenues.

This has made Amarin one of the most talked about potential targets for big pharma M&A this year, with Gilead Sciences Inc. and Pfizer Inc. the most frequently mentioned likely suitors. That is because Gilead is still in need of more M&A to help it replace its hepatitis C portfolio decline, and the company also recently added Vascepa to one of its NASH trials.

Meanwhile Pfizer is an even more obvious acquirer, having billions of dollars in its M&A war chest and a history in cardiovascular medicine with Lipitor (which remains a $1bn+ annual revenue blockbuster, even in a post-patent life).

AMARIN CEO ON TAKEOVER TALK

John Thero spoke to *Scrip* last week at the Jefferies conference in London, just as rumors of Novartis finalising a bid for The Medicines Company were circulating.

Thero was upbeat about Amarin's trajectory, but naturally insisted that securing the new label and then executing on its US marketing expansion was his sole focus.

Addressing takeover talk, he said: "The steps that we need to be taking as a management team are the same as to

CONTINUED ON PAGE 4

Ferring Enters Gene Therapy Fray
Teams up with Blackstone for bladder cancer candidate (p9)

Scrip Awards 2019
All the winners inside (p12-14)

Novartis's Latest Buy
The long farewell of The Medicines Company (p7)

from the editor

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As we race towards the end of the year, a flurry of acquisition and alliance deals are being signed and M&A rumors are swirling.

The spotlight is on the cardiovascular space, following the planned acquisition of The Medicines Company by Novartis, as reported last week. Amarin has been touted as a likely target before, and rumors are mounting again (see cover story).

Like The Medicines Company, Amarin is targeting the large population of patients for whom statins are unsuitable or insufficient. While its drug Vascepa is an already approved, relatively cheap pill taken two to four times a day, TMC's inclisiran is a twice-a-year RNAi injection that could improve patient compliance (a key factor in preventive treatment for "silent" conditions), with Phase III results in hand but yet to be approved. For more on Novartis's vision for inclisiran in the market place, see p4.

Unlike The Medicines Company with inclisiran not expected to have cardiovascular outcomes data until 2024, Amarin has already shown Vascepa can reduce the risk of cardiovascular events in high-risk patients, and an FDA advisory committee has recommended a label expansion to that effect.

Amarin is not the only company targeting the dyslipidemia market with an omega-3-based treatment – AstraZeneca will reveal the cardiovascular outcomes data for its own Epanova next year, and there are smaller players circling with late-stage candidates, including Acasti Pharma and Matinas BioPharma.

Regardless, the expected label expansion for Vascepa is likely to boost the product's sales substantially from the $380-420m forecast for 2019. Will its blockbuster potential attract a bidder before year-end?

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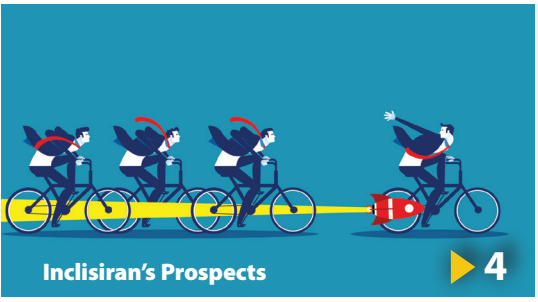

exclusive online content

Ipsen CBO: We Are Seeking Fresh Rare Disease Buys

STEN STOVALL sten.stovall@informa.com

Expect fresh initiatives in 2020 from Ipsen in the rare disease space, as the group continues to look for external innovation to help replenish its maturing pipeline, the Paris-based group's chief business officer said in an interview.

"External innovation is critical for our future growth because we don't really have in-house discovery research any longer; we're now really a commercial development powerhouse with global expertise in clinical development and commercialization and therefore really rely on external innovation to ensure that our pipeline stays strong and potent," Ivana Magovcevic-Liebisch told *Scrip*.

She was brought over in March 2018 as Ipsen's new dealmaker, moving over from US-based Axcella Health Inc. where she served as chief strategy and corporate development officer, and bringing a combination of expertise in corporate partnering, M&A, pipeline and product portfolio development, legal and IP strategy.

Magovcevic-Liebisch quickly became a key player in CEO David Meek's team of "drug scouts" to prioritize the search for opportunities and has a long history and deep interest in rare disease drug innovation. She played an important role in Ipsen's purchase of Canada's Clementia Pharmaceuticals Inc. in February 2019 for $1.04bn.

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To read the rest of this story go to: https://bit.ly/37ZRw3Y

inside:

CONTINUED FROM PAGE 1

whether we're a standalone company or someday bought by somebody, which is to create value."

He added: "Companies large and small get bought; I think the companies that end up looking for it are not necessarily the strongest. The best companies get bought, they don't get sold. So our focus is on creation of value."

Amarin's market capitalization currently stands at $7.4bn, which could attract takeover bids of around $10.4bn if it were to require the 41% premium Novartis paid for The Medicines Company.

As many commentators have observed, The Medicines Company is some way behind Amarin in proving the value of its product's impact on cardiovascular outcomes.

It expects to file inclisiran with the US Food and Drug Administration before the end of 2019, but its ongoing ORION-4 trial is not due to produce cardiovascular outcomes data until December 2024. This could make Novartis's goal of outperforming the lacklustre Repatha and Praluent more difficult, even given its more convenient twice-yearly dosing.

Amarin's CEO John Thero

POTENTIAL EUROPEAN PARTNERS

Meanwhile Amarin's Thero says his company has had "lots of enquiries" from companies interested in becoming its marketing partners in Europe.

Vascepa is due to be filed with the European Medicines Agency in early 2020, but is not likely to gain final approval until the end of next year.

"It's still bit early for us to be defining the commercial strategy in Europe or in particular partnering in Europe," commented Thero.

"We think that having a submission and advancing through the regulatory process will strengthen our hands relative to potential economic terms in a potential partnership. So, we're not yet at a point where we've kicked that off."

Amarin has endured very changeable fortunes since it was established in 1993, having faced skepticism about the therapeutic value of enhanced omega-3 products for years, especially after the failure of similar products such as GSK and Pronova's Lovaza.

The company is also facing challengers to its patent, such as Dr Reddy's, though analysts generally agree that the company has robust intellectual property which should keep out US generics until 2029.

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Novartis Sees Reimbursement Advantage For PCSK9 Launch

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Novartis AG is embracing a tough launch environment for cholesterol-lowering PCSK9 inhibitors with the $9.7bn acquisition of The Medicines Co. But Novartis believes the first-in-class small-interfering RNA (siRNA) drug inclisiran that it is acquiring has several advantages over the existing drugs on the market that will make it a blockbuster winner.

Those advantages include a more convenient dosing regimen, which will also translate to a lower cost, and a potentially more attractive reimbursement opportunity for physicians in the US under medical benefits/Medicare Part B.

CEO Vas Narasimhan outlined the strategic rationale for acquiring The Medicines Company for the rich price of $9.7bn during a conference call on 25 November, one day after revealing the deal had been struck. The chief executive also outlined the initial launch strategy for inclisiran, which the company expects will become a mega-blockbuster and one of the company's top-selling drugs.

Ramping from zero to $1bn-plus will require a more effective launch than what has been the experience with the two existing PCSK9 blockers on the market: Sanofi/Regeneron Pharmaceuticals Inc.'s Praluent (alirocumab) and Amgen Inc.'s Repatha (evolocumab). Those biologic drugs, on the market since 2015, are injected by patients at home every two weeks or once a month, while inclisiran is dosed just twice a year. The less frequent dosing is also expected to result in a more affordable price for treatment on an annual basis at least, though the company hasn't disclosed the pricing strategy.

Another potentially big commercial advantage for inclisiran over rivals could be around reimbursement in the US because Novartis believes that inclisiran, administered via two subcutaneous injections a year, will be administered in physicians' offices and thus largely reimbursed through medical benefits instead of pharmacy benefits, or Medicare Part B instead of Part D.

BUY-AND-BILL PAVING THE WAY FOR BROAD MARKET ACCESS

"We believe in the US, the ability to have a physician-administered product twice a year will enable us to launch through both the medical benefit under our potential buy-and-bill model, as well as the pharmacy benefit," Narasimhan said. "We believe under the medical benefit for primary care physicians who focus on cardiovascular patients, lipidologists as well as cardiologists, this is an attractive profile."

Twice yearly administration through Medicare Part B or private medical ben-

TURN TO PAGE 6

18th BIOSIMILAR MEDICINES CONFERENCE

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We are delighted to welcome you to our annual Biosimilar Medicines Conference, taking place on 26th and 27th March 2020 in Amsterdam, the Netherlands.

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The benefits already realised, thanks to the existing biosimilar regulatory and access policy frameworks in the EU, have materialised in greater access equity with undeniably Broader and Earlier Access to biological medicines in all countries, although the extent remains variable. Leveraging on this, discussions will focus on how to build healthy systems for healthier communities. A number of practical and concrete perspectives from stakeholders will illustrate policy intervention examples from different EU member states and the therapy area, including a deep dive into experience garnered in the field of rheumatology.

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CONTINUED FROM PAGE 4

efits will be less administratively burdensome versus the current requirements in offices. Reimbursement as a medical benefit could mean lower costs to the practices and a lower prior authorization burden, he added.

Under the Part B buy-and-bill model, physicians buy the drug and bill it after it is administered, which given the high costs of the drugs, offers some certainty around reimbursement. Providers are reimbursed at the average selling price (ASP) plus 6%, which can also present an inducement to administer the products in offices.

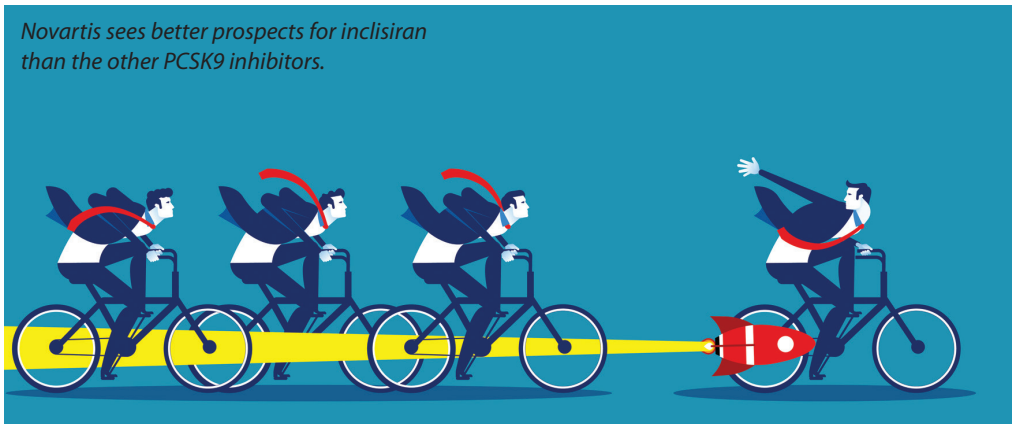
"We believe, in our model, 50% of relevant patients are in larger systems or larger IDNs [integrated delivery networks], with another 30% in medium-sized clinics and IDNs, all of which would benefit from having the ability to use the medical benefit," Narasimhan said.

The remaining 20% of patients are treated in smaller clinics, where Narasimhan conceded the company might have to do some more "heavy lifting" to get the offices in the buy-and-bill program.

Administration twice a year in a physician's office may also be more attractive to patients than regular at home injections, Narasimhan added, and the administration schedule every six months would be expected to line up with regular visits for patients with a cardiovascular risk profile. That could all result in better compliance and hopefully getting patients to reach their LDL-lowering goals, he pointed out.

THIRD TO MARKET BUT WITH ADVANTAGES

Praluent and Repatha tripped and fell over their own feet out of the starting gate when they launched in 2015. The commercial uptake of the drugs has been downright dismal, with a lot of the failure attributed to the high prices of the drugs – about $14,000 at launch – and payers' successful pushback through high copay requirements and burdensome category management requirements.



Novartis sees better prospects for inclisiran than the other PCSK9 inhibitors.

Sanofi reported €169m ($182.3m) in Praluent revenues in the first nine months of the year, with sales actually down 1.7%. Repatha has fared better, generating revenues of $461m in the first nine months of the year. Both Sanofi/Regeneron and Amgen have dramatically lowered the prices of their PCSK9 drugs since launch. Sanofi/Regeneron most recently cut Praluent's list price by 60% to $5,850 per year, on par with Repatha's lowered price.

PCSK9s are still an expensive treatment option versus generically available statins, the current standard of care for high cholesterol, though many patients still don't reach their goals with statins alone.

The launch of a safe and effective PCSK9 that is administered less frequently and costs less stands to be a big competitive threat to Repatha and Praluent, though Novartis paid handsomely for the near-term commercial opportunity and has yet to prove it can expand the use of PCSK9s to a substantially broader patient population. The other two drugs gained traction after completing cardiovascular outcomes trials, and inclisiran's ORION-4 outcomes trial is slated for completion in 2024.

"Our aspiration is to tackle the very, very large number of patients who need to get their cholesterol lowered," Narasimhan said. "We believe, based on everything that we've seen in the due diligence and our own independent research, there's high willingness to do this, and we can get this access program in place, and then enable broad access to this medicine."

The Medicines Company is expected to file the BLA for inclisiran in the US by the end of the year and in Europe in the first quarter of 2020, and Novartis is guiding investors to expect the first considerable commercial sales in 2021.

Novartis does bring substantial commercial experience in cardiovascular disease to the table, including building a brand in a challenging reimbursement environment. The company's experience with the heart failure medication Entresto has not been entirely dissimilar from the PCSK9 experience, in that an expensive medicine, even when supported by positive efficacy data, failed initially to find traction in the market. But Novartis has continued to build out the data around Entresto and deepen its penetration so that over many years, Entresto has grown into a blockbuster-sized drug.

"We believe with an incremental few hundred reps, we can support the launch of inclisiran, including a specialized force to enable Part B utilizations with the relevant health centers and providers," Narasimhan said. Novartis did not say how it plans to price inclisiran but Narasimhan said "responsible" pricing in line with value frameworks would be an important element of a successful launch.

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It Has Been A Long Farewell To The Medicines Company

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Novartis AG's acquisition of The Medicines Co. for $9.7bn is a healthy exit for the company's investors, but the company Novartis is buying is a streamlined, unrecognizable version of the hospital specialist The Medicines Company once was.

In less than five years, The Medicines Company went through a dramatic makeover, transitioning from a multi-product, revenue-generating drug company to a single asset drug developer on the quest for a buyer.

Now the company's product is poised to be integrated into Novartis, and The Medicines Company will wind down after 23 years of business. The Swiss pharma announced it had struck a deal to acquire the company on 24 November.

Clive Meanwell, The Medicines Company's founder and longtime CEO, was the architect behind the company. He founded The Medicines Company in 1996, with the financial backing of investment firms MPM Capital and Warburg Pincus, to develop late-stage drug candidates shelved by bigger biopharmas. Over the next 20 years, he built the company into a multi-product hospital specialist, generating hundreds of millions in sales, largely through acquisition.

One of the first candidates Meanwell brought in was the company's eventual best seller, bivalirudin, the drug that became Angiomax, which it gained through a licensing deal with Biogen Inc. in 1997 for $30m up front. The company had eight employees at the time. It went public in August 2000, and Angiomax was approved by the US Food and Drug Administration months later.

Meanwell stepped aside late last year, however, to make way for a new CEO, Mark Timney, to be the architect of a different strategy: to broker a sale. By then, the company had an activist investor, Alex Denner, chairing its board and had sold off all of its commercial-stage drugs to focus investment on the development of its sole clinical candidate, the Phase III RNA-interference drug inclisiran for high cholesterol. That's the drug Novartis believes it can commercialize into a mega blockbuster.

Inclisiran came into the company's portfolio in February 2013 through a development and commercialization alliance with Alnylam Pharmaceuticals Inc.. Under the agreement, The Medicines Company paid just $25m up front in cash and agreed to pay $180m in development and commercial milestone fees, and royalties on sales. The Medicines Company was responsible for leading and funding development from Phase II.

That deal turned out to be a pivotal turning point for the company. As commercial prospects for some of the company's other big sellers dried up and development assets fizzled, investors focused the lens increasingly on inclisiran.

The Medicines Company's revenues peaked in 2014, when the company generated $724.4m in revenues, driven largely by the blood thinner Angiomax (bivalirudin) and other products like the surgical clot promoter Recothrom (thrombin) and new antibiotic launches Orbactiv and Minocin (minocycline). Angiomax, a blood thinner used during percutaneous coronary intervention (PCI) procedures, was the company's crown jewel. It generated the vast majority of sales, $635.7m in 2014, and The Medicines Company's growth strategy hinged on its continued success. Patent challenges from generic drug makers cast a long shadow over that strategy, however, and in 2015 it crumbled altogether when an appeals court ruled rival Hospira Inc.'s generic drugs did not infringe The Medicine Company's patents. In an enormous blow to the company, generic versions of Angiomax launched four years earlier than expected.

Meanwhile, another drug the company was developing faced a setback around the same time – Kengreal (cangrelor). The drug was approved by the FDA in June 2015 as an adjunct to PCI to reduce the risk of myocardial infarction, repeat coronary revascularization and stent thrombosis, but only in a narrow patient population, a disappointment for its commercial prospects.

The company also had invested substantially in the development of novel antibiotics, including with the 2013 acquisition of Rempex Pharmaceuticals Inc. for $140m up front plus earn-outs. That deal eventually led to the FDA approval and launch of Vabomere (meropenem/vaborbactam) for complicated urinary tract infections, but the commercial dynamics for novel antibiotics are challenging.

After the Angiomax patent ruling, the company immediately halted promotional activities, redeployed some sales reps and cut 100 employees to reduce costs. Its revenues in 2015 declined by more than half, to $309m. By 2017, the company's revenues were only $44.8m as the company had by then pivoted to a new strategy that really began with that court decision.

"It's time for us to move on, and we have," Meanwell said during the company's second quarter earnings call in 2015, weeks after the court ruling. He then mentioned an idea that would solidify into a core part of the company's strategy for the next three years – partnering and divesting assets.

"We're seeking partners for global and/or ex-US investment in our new products and R&D programs," he said. "With Angiomax uncertainty now resolved, we believe we can secure deals that advance our pipeline, defray development expenses, expand the clinical and commercial potential of our products and create value for our shareholders."

In 2016, the company sold much of its cardiovascular portfolio to Chiesi Farmaceutici SPA, including Kengreal, Cleviprex (clevidipine) and argatroban, in exchange for $264m in cash and $480m in sales-based milestone payments.

In November 2017, after The Medicines Company moved inclisiran into Phase III clinical development, the company reached a deal to sell its infectious disease business to Melinta Therapeutics Inc. for $270m in cash and stock. The antibiotics specialist is now facing financial uncertainty, suggesting that The Medicines Company made a savvy decision exiting the space.

Now what's left of the company is poised to be sold to Novartis, and for a lot of money. Novartis believes inclisiran, as a more convenient, more affordable PCSK9 option, will become one of its best sellers. The Medicines Company's management has indeed executed on that plan to create value for shareholders, though not the way it had initially intended.

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Asahi Paying $1.3bn For One-Product Veloxis

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Asahi Kasei Corp. is to launch in December a DKK6 ($0.88) per share voluntary tender offer for Veloxis Pharmaceuticals AS (formerly LifeCycle Pharma), a one-product company focused on post-transplant therapy.

The move, which Veloxis said followed a strategic review and competitive bidding process, has been prompted by the large diversified Japanese group's desire to build its strategic position in the health sector, for which it sees stable long-term growth.

Its main goal through the deal is to acquire a presence in the US pharma market, where the company said it had been seeking acquisition opportunities.

> "In order to grow into a diversified company, we would need to make significant additional financial investment, which brings with it clinical and regulatory risk." – Michael Thomas Heffernan.

Copenhagen-based Veloxis was founded in 2002 as a spin-off of major Danish pharma firm Lundbeck Inc., a major shareholder in the Nasdaq Copenhagen-listed venture.

Veloxis chairman Michael Thomas Heffernan told a conference call that the company is expected to continue under its current name and the leadership of CEO Craig Collard, himself a US citizen and founder of Cornerstone Therapeutics, sold to Chiesi Farmaceutici SPA in 2014 for around $107m.

"In order to grow into a diversified company, we would need to make significant additional financial investment, which brings with it clinical and regulatory risk," he commented.

Asahi made the most attractive offer based on all valuation methodologies, and will provide the financial resources and expertise to move forward, he added.

DEAL SPECIFICS

The total equity value of the deal is JPY143.2bn ($1.31bn), which Asahi said would be funded by a mix of cash on hand and bank loans.

The tender offer compares with Veloxis' share price of DKK6.60 just prior to the announcement and reflects some recent volatility, representing a 6% premium over the 30-trading day volume weighted average share price.

Major investors and the management of Veloxis, which together own 81.2% of the firm (including 36.6% each held by Lundbeckfond Invest and Novo Holdings), have already signed irrevocable agreements to sell their shares and warrants at DKK4.45 per share.

The higher price for minority shareholders reflects recent rises in the price, driven by a brighter outlook for Veloxis this year.

The company had sales of $39.5m and an operating loss of $5.8m in calendar 2018, but expects revenues to surge to $75-82m and to move into profit this year.

With a wholly owned US subsidiary in Cary, North Carolina, Veloxis' current business is based solely around Envarsus XR, a once-daily extended release formulation of tacrolimus, used to prevent rejection in kidney transplants in combination with other immunosuppressants.

The drug, a value-added generic version of Astellas Pharma Inc.'s Prograf, uses the Danish firm's proprietary MeltDose oral delivery technology, which improves and evens out bioavailability and helps reduce side-effects.

In its rationale for the transaction, Asahi noted there around 20,000 kidney transplants are performed annually in the US.

BUILDING HEALTH CARE

Asahi, a large chemicals and materials group, also sees the Veloxis deal as providing a platform for drug licensing activity, along with improved access to innovation and clinical practice in the US and a route to developing new products targeting US medical needs.

Asahi's current health interests include drugs and devices, and its Health Care division accounted for 15% of group net sales in fiscal 2018, generating JPY316.2bn, but some 19% of total operating income.

The existing drug business is very much focused on Japan however, and includes portfolios across bone disorders, immunology and neurology, including Teribone (teriparatide) for osteoporosis.

The strategic aim now, the company said, is to globalize the division with a focus on the US hospital/specialist sector - the mid-term target is for sales of JPY600bn and operating income of JPY80bn for the Health Care business.

MITSUBISHI, SHIONOGI IN OTHER DEALS

The Asahi deal follows other end of year action in the Japanese pharma sector, where Mitsubishi Chemical Holdings Corp. has recently launched a tender offer to completely buy out its 56.4%-held pharma operation Mitsubishi Tanabe Pharma Corp. (MTP).

MTP shares would be delisted as the wider group seeks synergies from bringing together its diversified businesses under one roof.

The JPY2,010 per share buyout offer is valued at JPY491.8bn ($4.51bn) and represents a 50% premium to the share price before the announcement.

Mid-sized pharma firm Shionogi & Co. Ltd. is meanwhile in the process of acquiring listed Japanese vaccine specialist UMN Pharma Inc., which is developing flu, rotavirus and norovirus vaccines.

Shionogi is already the main shareholder, owning around 20% of UMN as of the end of June, and the buyout is valued at around JPY6.65bn.

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Ferring And Blackstone Launch Gene Therapy Company

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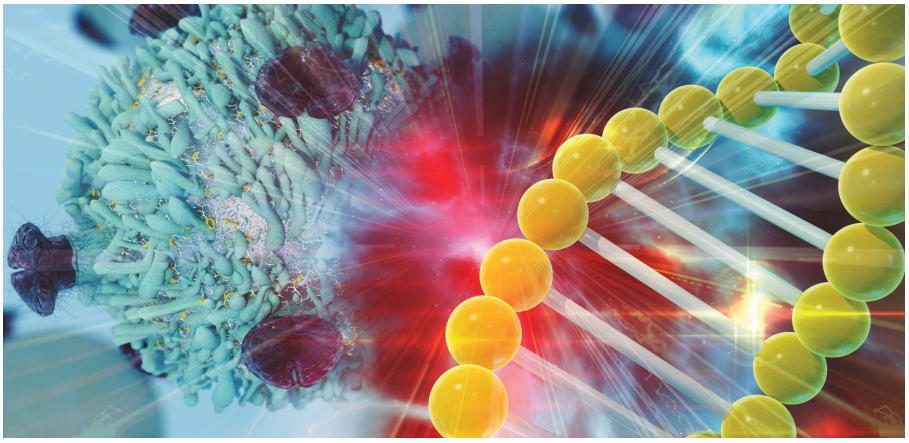
Ferring Pharmaceuticals AS has teamed up with private equity group Blackstone Life Sciences to create FerGene, a new company backed with over $570m to advance its investigational bladder cancer gene therapy nadofaragene firadenovec to the US market.



Blackstone is putting in $400m and Ferring will invest up to $170m in FerGene to advance nadofaragene firadenovec, which is in late-stage development for patients with high-grade, Bacillus Calmette-Guérin (BCG) unresponsive, non-muscle invasive bladder cancer (NMIBC). The privately owned Swiss firm licensed the therapy from Finland's FKD Therapies OY in May 2018; its biologics license application has been accepted for filing by the US Food and Drug Administration and been granted a priority review.

Ferring is best known as a leader in reproductive medicine and women's health and has decided that rather than going it alone with the gene therapy or sharing it with another pharmaceutical player, it sees more value in plumping for a private equity partner. Chairman Frederik Paulsen said, "Bringing a novel gene therapy to the market requires dedicated focus and capabilities," and FerGene, which will operate under the Ferring umbrella, "will have the resources and team needed to help us potentially bring nadofaragene firadenovec to patients."

Ferring told *Scrip* that as well as providing capital, Blackstone provided "operational, clinical, regulatory and commercialization expertise to help give late-stage product candidates the best likelihood of success." The firm added that by leveraging its "industry leadership, longstanding relationships around the globe, and ability to commit capital at scale, Blackstone was uniquely situated for this partnership with Ferring."

Blackstone only recently scaled up in healthcare formally with the acquisition of life sciences investment firm Clarus in November last year, but the group, which has around $500bn in assets under management, has quickly made its mark. Its life sciences team includes experts such as Barry Gertz (former global head of clinical development at Merck & Co. Inc.), Ed Scolnick (ex-president of Merck Research Labs), Dennis Henner (former global head of research at Genentech Inc.) and Paris Panayiotopoulos, ex-CEO of Ariad Pharmaceuticals Inc., the oncology firm sold to Takeda Pharmaceutical Co. Ltd. in 2017 for $5.2bn.

In late February this year, Blackstone invested $250m to create a cardiovascular start-up called Anthos Therapeutics Inc. in partnership with Novartis AG. As part of that deal, the latter licensed a Phase II-ready anti-Factor XI/XIa monoclonal antibody codenamed MAA868 to Anthos, which the firms said represented a promising next-generation antithrombotic investigational therapy with the potential to prevent multiple thrombotic diseases with minimal or no bleeding risk. *(Also see "Finance Watch: VC Mega-Deals Launch Biopharma Firms With New Takes On CV, Genetic Diseases" - Scrip, 5 Mar, 2019.)*

Blackstone also has its eye on the Japanese market. In March, it announced plans to buy the private specialty firm Ayumi Pharmaceutical, which specializes in the manufacture and sale of pain, rheumatism and orthopedic drugs. *(Also see "Blackstone Bets On Pharma In First Japan Buy, But Why?" - Scrip, 26 Mar, 2019.)*

The FerGene deal is structured in a different way to the Anthos venture and Ferring intends to commercialize nadofaragene firadenovec outside the US. Phase III results of the drug, which has been studied in in 33 centers across the US, will be presented at the Society of Urologic Oncology meeting in Washington DC on 5 December.

Ferring has high hopes for nadofaragene firadenovec, which is administered by catheter and enters the cells of the bladder wall. In Phase II trials, 35% of BCG-unresponsive NMIBC bladder cancer patients who were given one dose every three months were free of high-grade disease at one year.

SIZEABLE MARKET

Speaking to *Scrip* last year, Ferring chief medical officer Klaus Dugi said that in high-grade NMIBC patients, while BCG is effective, over 60% of cases eventually re-occur and the outcome for such patients is poor, with total cystectomy (complete removal of the bladder) to prevent the cancer spreading to other organs generally being the next option. There are around 430,000 new cases of bladder cancer reported worldwide each year and Dugi pointed out that it was also the fourth most common cancer in men in the US and the most expensive to treat on a life-time basis.

These are interesting times for Ferring. It is in pole position to be first pharmaceutical company to file a treatment that harnesses the power of the human microbiome, with a potential launch pencilled in next year for RBX2660 for reducing recurrent *Clostridioides difficile* (*C diff*) infection in adults. *(Also see "Ferring Favorite To Get First Approval For Microbiota-Based Therapy " - Scrip, 8 Jul, 2019.)*

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ImmuPharma Soars On Avion Lupus Deal

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In a spectacular reversal of fortunes, ImmuPharma PLC has seen its stock treble after inking a licensing deal with Avion Pharmaceuticals LLC potentially worth almost $100m for Lupuzor, the UK biotech's lupus drug which had been written off by many observers.

The pact will see Avion fund the full expected costs of the new Phase III trial up to $25m for Lupuzor (forigerimod), ImmuPharma's first-in class autophagy immunomodulator which has had a tricky time in the clinic. In April last year, the company presented data from an initial analysis from a Phase III trial which showed that Lupuzor plus standard of care (SOC), such as steroids, antimalarials and methotrexate, was more effective than placebo plus SOC (52.5% versus 44.6%). However the high response rate in the placebo group meant the primary endpoint of statistical significance was not reached.

That news was greeted by some analysts as the end for Lupuzor but ImmuPharma continued to have faith, pressing on with further data analysis from the study. It demonstrated that in the European cohort (130 patients), Lupuzor plus SOC showed statistically significant reductions (71.1% vs 48.8%) in disease activity compared to placebo plus SOC in 79 patients (60.8 %) who were anti-dsDNA autoantibody positive.

In June this year, ImmuPharma presented details of a 62-patient, 24-week open-label extension, "confirming the outstanding and robust safety profile of Lupuzor whilst also reporting no serious adverse events." The results also revealed that 32% of patients were in remission by the end of the study.

Following these analyses, the company believes it has the ability to select the most responsive patients by biomarker profile and a new Phase III trial design has been identified. In return for funding the study, which will begin next year following agreement of the design between the partners and the US Food and Drug Administration, Avion is getting full US licensing rights for Lupuzor, while ImmuPharma will receive milestone payments and tiered double-digit royalties up to 17%.

Specifically, the AIM-listed company is in line for a $5m payment on regulatory approval of Lupuzor in lupus, and $65m on the achievement of overall sales targets. ImmuPharma will also receive $5m for each additional approval as Avion also has the US rights to explore further opportunities for other auto-immune indications.

Since 2012, Avion has launched more than 55 new drug candidates and over 20 generic product extensions. It is best known as a dietary supplements seller, but ImmuPharma claimed that Avion's launch earlier this year of Romeg Therapeutics' Gloperba, the first liquid formulation of colchicine approved by the FDA for gout flares for adults "is an excellent sales and marketing fit for the future commercialization of Lupuzor, as rheumatologists are the core prescribers and therapeutic influencers in both gout and lupus."

Avion CEO Art Deas said that "after in-depth due-diligence around Lupuzor, its mechanism of action and learnings within the initial Phase III results, we believe [it] has a unique position within lupus that sets it apart from competition, and we are delighted to be extending our footprint within this therapeutic area. With approximately 1.5 million patients in the US suffering from lupus, there is a significant unmet need for a safe and effective drug."

Investors were equally enthusiastic and ImmuPharma's shares closed up a whopping 297% on 28 November to £0.28.

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AC Immune CEO Outlines 'Roadmap' For Fighting Alzheimer's

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AC Immune SA and its pharmaceutical partners are following a five-point strategy for advancing its pipeline of Abeta- and Tau-targeted therapies in Alzheimer's Disease, and coming data readouts should offer multiple catalysts for the Swiss biotech's stock, its CEO told *Scrip*.

FIVE-POINT ROADMAP

Andrea Pfeifer outlined her five-point "Roadmap" to successful therapies for neurodegenerative diseases that recognizes the importance of treating earlier, targeting Tau, focusing on more homogeneous populations, precision medicine using diagnostics, and exploring neuro-inflammation as a target. The approach's first priority, she said, is early testing.

"One thing the neurodegenerative community now agrees on is the need to treat early, simply because the longer that you wait to treat, the more neurons, which are irreplaceable, die. The best outcomes are there when preventative action is taken,

rather than to treat once symptoms have already appeared," Pfeifer said.

The targeting of Tau, and the eventual use of combination therapies will also be part of the future treatment for neurodegenerative diseases.

"At this stage of our knowledge, combination therapy certainly involves Abeta and certainly involves Tau, and it might involve inflammation because one of the components in between Tau and Abeta is apparently inflammation, so targeting Abeta, Tau and inflammation might be the cocktail for future treatment," Pfeifer said.

Her NASDAQ-listed clinical-stage biopharmaceutical company aims to become a global leader in precision medicine for neurodegenerative diseases. It uses two proprietary discovery platforms, SupraAntigen and Morphomer, to design, discover and develop small-molecule and biological therapeutics, as well as diagnostic products, intended to diagnose, prevent and modify neurodegenerative diseases caused by misfolding proteins.

AC Immune's pipeline features nine therapeutic and three diagnostic product candidates, with four therapies and one diagnostic in Phase II. It has collaborations with big pharma groups including Genentech Inc., Eli Lilly & Co. and Janssen Pharmaceuticals Inc..

"Our science and our partnerships have given us the world's biggest neuroscience pipeline," Pfeifer said.

"We expect multiple catalysts in 2019 and 2020, highlighted by Phase II data for semorinemab, our anti-Tau antibody partnered with Genentech, which we believe will be the first Phase II data available for a Tau-targeted therapy in Alzheimer's disease. We also expect further progress across our development pipeline with both early- and late-stage data readouts that we believe will build substantial value for the company," she said.

INCLUDES HOMOGENEOUS PATIENT POPULATIONS

The Swiss company needs some good news after suffering a big setback earlier this year with the failure of two Phase III studies, CREAD-1 and CREAD-2, in Alzheimer's disease, which showed lack of efficacy of the investigational monoclonal antibody crenezumab. *(Also see "AC Immune/Roche Drop Crenezumab After Phase III CREAD Alzheimer's Failure" - Scrip, 30 Jan, 2019.)*

"One thing the neurodegenerative community now agrees on is the need to treat early, simply because the longer that you wait to treat, the more neurons, which are irreplaceable, die." – Andrea Pfeifer

Pfeifer said crenezumab could still become AC Immune's first commercialized product if a separate clinical study of crenezumab taking place in Colombia, South America, succeeds within a patient group with a genetic predisposition to Alzheimer's.

The study, begun in December 2013 and funded by the US National Institutes of Health, involves around 300 people from an extended family in Colombia who share the risk from a rare genetic mutation that triggers Alzheimer's symptoms around 45 years of age.

The trial presents unique opportunity to study prevention and treatment in a defined population. It was set up under the public-private partnership, the Alzheimer's Prevention Initiative, and is a collaboration between the US's NIH, the Banner Alzheimer's Institute (BAI) headquartered in Phoenix, AZ, the University of Antioquia in Colombia, and Genentech (Roche). It is expected to complete in the first quarter of 2022.

"AC Immune doesn't have a product on the market yet - but crenezumab might become our first if this study works out in 2022. And as it's for an orphan indication, the drug, in a perfect world, could in that case be on the market by 2023," Pfeifer said.

She said use of homogeneous populations goes hand in hand with use of precision medicine.

"Precision medicine is needed in order to treat people with their underlying protein pathology. By using a genetic population like our Colombia study, we are working in an environment that is much more defined and offers a much more homogeneous situation which allows for more favorable statistics," she explained

The CEO said she was particularly excited about another study testing use of the anti-Abeta therapeutic vaccine known as ACI-24 in people with Down's syndrome, a population at high risk of developing Alzheimer's Disease.

The Phase Ib is targeting misfolded Abeta and follows compelling memory enhancement in Down's syndrome mouse models. Between 75% to 100% of people with Down's syndrome have Alzheimer's by age 60, according to AC Immune.

"This is the world's first clinical trial for a vaccine targeting Abeta in people with Down's syndrome and could prove very important. It would be a dream come true if an underprivileged population like this could have their independence extended," Pfeifer said.

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AstraZeneca and Galapagos Shine At The 15th Annual Scrip Awards

The pharma, biotech and allied industries came together in London on 4 December to celebrate another year of achievement at the 15th Annual Scrip Awards, hosted by the broadcaster Fiona Bruce.

The 21st century is truly shaping up to be biopharma's golden age. With innovation in so many fields, from scientific progress in academia through the discovery of novel therapies to the use of big data, real-world evidence, artificial intelligence and other evolving tools, R&D has never been so diverse nor so exciting. And this year's Scrip Awards rewarded excellence in all aspects of the industry's activities over the past year.

The Scrip Awards categories range from those that applaud the broader achievements of companies, to those for innovation in deal making, advances in R&D and the more personal accomplishments of teams and individuals. New this year, we introduced **MSD's Innovation Award** to acknowledge outstanding scientific or technological breakthroughs that have transformative potential for the discovery or development of new medicines.

The night's biggest winner was AstraZeneca, which took three trophies back to Cambridge: the **Worldwide Clinical Trials' Licensing Deal of the Year Award** for its five-part deal including monalizumab with Innate Pharma in immuno-oncology; the award for **Executive of the Year – For Large & Medium Cap Companies**, which went to Menelas Pangalos, EVP and president, R&D BioPharmaceuticals; and **Medidata's Community Partnership of the Year Award** for AstraZeneca's Energy Challenge.

The evening's other big winner was Galapagos, which won **WuXi AppTec's Biotech Company of the Year Award** and the **Financing Deal of the Year (sponsored by Bioclinica)**. But the night belonged to Jane K Osbourn OBE, the recipient of **Scrip's Lifetime Achievement Award (sponsored by ICON)**.

COMPANY AWARDS

The winner of the **Pharma Company of the Year award** is chosen each year by *Scrip*'s senior editorial team, based on a variety of key metrics, including its financial performance in the previous year, strategic advances, progress in the emerging markets, and advances in the drug pipeline.

This year the honor went to Takeda Pharmaceutical Co Ltd, a company that made global headlines for its audacious $62bn acquisition of Shire, completed early this year. While the deal accelerated the Japanese firm's entry into the global top 10, broad transformation was already underway under French CEO Christophe Weber, who has overseen multiple restructuring and divestment efforts while honing focus on core therapeutic areas.

Meanwhile, its GI drug Entyvio (vedolizumab) continues to earn its blockbuster credentials, while access to external innovation through multiple alliances has helped build the clinical pipeline. The company also deserved recognition for its diversification and inclusion efforts at the highest levels, and for pursuing transparency and honesty with stakeholders, investors and the media, as it seeks to become a truly global operation with Japanese roots.

Masters Speciality Pharma's Best Company in an Emerging Market Award went to Chinese firm BeiGene. The Beijing-based firm achieved a number of significant milestones to cement its reputation as the bellwether Chinese biotech: it completed a secondary offering on the Hong Kong Stock Exchange, raising HK$7.3bn ($933m); signed five unique partnerships including the "three-in-one" deal with Zymeworks; and had regulatory filings for tislelizumab and zanubrutinib accepted by China's National Medical Products Administration.

The judges were impressed with "up-and-coming" BeiGene, saying this was "a significant year in the development of this rapidly growing business."

For the categories recognizing CROs, ICON won the **Best Contract Research Organization – Full-Service Providers** trophy, just edging out highly commended PPD in a very tight race.

ICON contributed to the development of 21 new drugs in 2018/19 and exceeded sponsor expectations, beating industry medians through strong collaboration and detailed planning during start-up, careful site selection and monitoring progress of enrolment and in-depth global regulatory expertise.

The judges lauded it for making major strides to enhance its capabilities in patient recruitment and retention, adaptive clinical trials, real-world evidence, precision oncology and various IT/automation tools. "Very good innovations such as for developing protocols, smart database design and real-world data – also strong on developing innovation through collaboration for example with real-world data," they said.

Meanwhile the Award for **Best Contract Research Organization – Specialist Providers** went to Quanticate, one of the world's largest CROs focused on the collection, analysis and reporting of clinical study data with a high level of expertise for biometrics. The judges were won over by its interesting range of novel technologies employed to support clients, and said it delivered "impressive results" to sponsors.

WuXi AppTec's Biotech Company of the Year Award went to Galapagos after a critical 12 months which put it firmly on its way to become a fully integrated biopharmaceutical company. 20 years after its inception, 2018 saw Galapagos finish its first Phase III trial for filgotinib and prepare its first filing for the JAK1 inhibitor in rheumatoid arthritis in the EU this summer.

The judges commended the Belgium-based firm for its "sustained and patient commitment that continues to build on its foundation, creating ever greater value."

DEAL MAKERS

Galapagos's **Financing Deal of the Year (sponsored by Bioclinica)** win was for its $345m secondary follow-on financing in September 2018, which fulfilled its financing goal of raising an additional year of R&D spend, following the announcement of first and very positive

Phase III results with its lead program filgotinib. The transaction was completed in seven hours, at a price 29% higher than the previous fundraising.

Deal-making is at the heart of the pharma and biotech industries and the categories here seek to reward the full range of activities. **Worldwide Clinical Trials' Licensing Deal of the Year Award** went to Innate Pharma and AstraZeneca for their five-part deal including monalizumab in immuno-oncology. Beating off strong opposition, this novel, complex and strategically important five-part licensing and investment deal garnered most praise from the judges.

It strengthened a leading immuno-oncology collaboration while accelerating the corporate strategies of both companies. AstraZeneca secured a constant stream of innovation with Innate's anti-NK2Ga mAb, monalizumab, and CD39 mAb program, while Innate acquired the launch-ready asset Lumoxiti, which will transform it into a commercial company.

While the clinical value of each asset remains to be determined, the judges felt it to be a transformative deal of many moving parts. "A very complex deal to negotiate with all the various parallel components, must have been a nightmare for the BD team to manage, well done!"

The trophy for **Best Partnership Alliance (sponsored by CMIC)** went to CRUK, LifeArc and Ono for their Cancer Immunotherapy Alliance. This multimillion pound strategic partnership brought together Cancer Research UK, the medical charity LifeArc and Ono Pharmaceutical Co in a unique alliance that relies on the complementary expertise of each partner to progress research into new immuno-oncology drug targets. It provides a clear path for the development of drug targets identified by the research community supported by investment from Ono and LifeArc.

The judges liked the fact that two charitable organizations had overcome the challenges of marrying charity and profit-based entities in a three-way alliance with an industry player that must have been tricky to negotiate. They described it as an "alliance bringing together the differential skills and strengths of three reputable organisations."

2019 Scrip Awards Winners

Scrip's Lifetime Achievement Award (sponsored by ICON)	Jane K Osbourn OBE
Pharma Company of the Year	Takeda Pharmaceutical Co Ltd
Syneos Health's Best New Drug Award	Alnylam Pharmaceuticals' Onpattro (patisiran) for polyneuropathy of hereditary transthyretin-mediated amyloidosis
WuXi AppTec's Biotech Company of the Year Award	Galapagos
Medidata's Community Partnership of the Year Award	AstraZeneca's Energy Challenge
IQVIA's Clinical Advance of the Year Award	Novartis/AveXis's Phase III STR1VE study of Zolgensma in spinal muscular atrophy
Executive of the Year – For Large & Medium Cap Companies	Menelas Pangalos, EVP and president, R&D BioPharmaceuticals, AstraZeneca
Executive of the Year – For Small Cap and Private companies	Ryan Cawood, founder and CEO of Oxford Genetics
Masters Speciality Pharma's Best Company in an Emerging Market Award	BeiGene
Worldwide Clinical Trials' Licensing Deal of the Year Award	Innate Pharma and AstraZeneca's five-part deal including monalizumab in immuno-oncology
Business Development Team of the Year (sponsored by Skipta)	Procter & Gamble's Business Development Team
Best Contract Research Organization – Full-Service Providers	ICON
Best Contract Research Organization – Specialist Providers	Quanticate
Best Partnership Alliance (sponsored by CMIC)	CRUK, LifeArc and Ono Cancer Immunotherapy Alliance
Financing Deal of the Year (sponsored by Bioclinica)	Galapagos's $345m secondary follow-on financing
Best Technological Development in Clinical Trials	CluePoints' Risk-Based Study Execution and Data Quality Oversight Software for Clinical Trials
MSD's Innovation Award	Mogrify's direct cellular conversion technology

Medidata's Community Partnership of the Year Award went to AstraZeneca's Energy Challenge, the company's biggest ever STEM Outreach programme, which is run in partnership with local schools. Created by AstraZeneca scientists from scratch, with the objective of engaging pupils at the critical age of 9-10 years when they are most at risk of switching off from science, The Energy Challenge schools competition has run in 70 primary schools across the Cambridgeshire region.

The judges described it as a a good approach to stimulate young people to have an interest in STEM – important in encouraging the next generation of researchers – and liked the fact it was not related to promoting the AstraZeneca business. "This looks like a good program engaging youngsters in science and making it real for them. Seems to have had real impact!"

R&D DELIGHTS

Moving on to the Awards categories based around research and development, Alnylam Pharmaceuticals' Onpattro (patisiran) won **Syneos Health's Best New Drug Award**.

In August 2018, Alnylam made history with the first US Food and Drug Administration approval for an RNA interference (RNAi) therapeutic, Onpattro, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, a disease which previously had no FDA-approved therapies.

The development and approval of Onpattro has opened the doors for RNAi to become a new way to develop medicines,

as monoclonal antibodies once did in the 1990s. "There has been much skepticism about RNAi therapies and Alnylam deserves credit for leading and persisting with this platform technology," said the judges. "Onpattro represents a first-in-class treatment for hATTR and will be an important drug for patients with this highly unmet medical need."

At the other end of the drug development process, this year's new category, **MSD's Innovation Award**, seeks to reward just such kinds of paradigm-shifting technologies that led to the approval of Onpattro.

In a tightly fought category, the winner was Mogrify's direct cellular conversion technology, which allows the transformation of any human cell type into any other without having to go through a pluripotent stem cell or progenitor cell state.

Although still early, this technology opens up the opportunity to develop and scale up any autologous and allogeneic cell therapies across every therapeutic area, as well as to create a new class of therapies: in vivo reprograming.

The judges also commended highly Lyndra Therapeutics' ultra-long acting pill, which was described as a "potential game-changer."

Novartis/AveXis's Phase III STR1VE study of Zolgensma in spinal muscular atrophy was named the winner of **IQVIA's Clinical Advance of the Year Award**.

Data presented at the American Academy of Neurology meeting in May from the ongoing Phase III STR1VE trial of a one-time IV infusion of of Zolgensma in type 1 SMA showed that of 15 patients who reached 13.6 months of age or discontinued the study prior to 13.6 months of age, 13 (87%) survived without permanent ventilation. Untreated natural history indicates that only 25% of babies with type 1 SMA will survive event-free by the time they reach 13.6 months of age.

One of our judges summed up the feeling around these data: "As a former pediatric intensive care nurse I had patients with this disease, who lived their entire lives completely paralyzed and ventilated from early infancy. This is an absolutely transformative potential treatment... This is what all clinical researchers sign up for, a passion to make a difference in patients (and families) lives."

Clinical studies depend for their efficient running on continual advances in specialist support software. The Scrip Award for **Best Technological Development in Clinical Trials** is designed to celebrate these advances and was won this year by CluePoints' Risk-Based Study Execution and Data Quality Oversight Software for Clinical Trials.

CluePoints champions the use of automated statistical techniques to interrogate clinical and operational data sets, allowing sponsors, CROs and partners to address the challenges and opportunities of good clinical practice guidelines. "This is a very useful technology for compliance with ICH GCP R2.2," the judges said.

PEOPLE MATTER

Finally, the pharma, biotech and allied industries are nothing without the excellent people working within them, and the Scrip Awards has a number of categories to celebrate both individual and team achievement.

The **Business Development Team of the Year (sponsored by Skipta)** trophy went to Procter & Gamble's Business Development Team. This team successfully negotiated the P&G acquisition of Merck Consumer Health providing P&G with all the capabilities it lost with the dissolution of the PGT Healthcare Partnership between P&G and Teva. It also gained a fast-growing portfolio of brands that offered P&G accelerated OTC growth, a stronger geographic footprint and a more balanced portfolio.

"A good story and a pressing need, plus imaginative solutions to boot," said the judges.

AstraZeneca's EVP and president, R&D BioPharmaceuticals, Mene Pangalos, was named **Executive of the Year - For Large & Medium Cap Companies**, for his efforts in turning AstraZeneca's R&D around to a point where new medicines formed a big part in the company's return to growth in 2018.

Pangalos has been a key driving force behind a near five-fold increase in AstraZeneca's R&D success rate since 2012 by instilling a culture shift that brought back scientific rigor to the forefront of the discovery process. The judges described him as a "dynamic leader driving dynamic initiatives," and said he had produced a "good evolution that deserves to be recognized."

Turning to smaller companies, Ryan Cawood, founder and CEO of Oxford Genetics, won the **Executive of the Year – For Small Cap and Private Companies**.

Cawood successfully oversaw six new licensing deals in the past year for Oxford Genetics' new scalable gene therapy manufacturing technologies, establishing the firm within the biotech industry. "A classic entrepreneur and renaissance man who should continue to rise and achieve the scale," said the judges.

SCRIP'S LIFETIME ACHIEVEMENT AWARD

The highlight of the evening was the presentation of **Scrip's Lifetime Achievement Award (sponsored by ICON)** to Jane K Osbourn OBE for a career that has spanned academia and industry.

An expert in antibody engineering, Osbourn originated several key publications and patents, and also made a significant contribution to the discovery and development of the world's bestselling drug, Humira, and the first lupus therapy in 50 years, Benlysta, plus more than 40 clinical candidates.

After obtaining a first-class degree in natural sciences (biochemistry) from the University of Cambridge, she completed a PhD at the John Innes Centre for Plant Science Research in Norwich. This was followed by a post-doctoral position at Rutgers University in New Jersey, before a move into medical research through a British Heart Foundation post-doctoral fellowship at the department of medicine at Addenbrooke's Hospital in Cambridge.

In 1993, Osbourn joined Cambridge Antibody Technology, which was acquired by AstraZeneca in 2006 and merged into MedImmune a year later to form AZ's biologics arm. She worked there across many therapy areas and led a number of global teams focused on the development of antibody therapies.

She is chair of the board of directors of the BioIndustry Association, a director of Babraham Bioscience Technologies and a director of Cambridge Enterprise and has presented at a number of parliamentary Select Committees in the UK. Osbourn was awarded an OBE in the 2019 Queen's Birthday Honours for services to human monoclonal antibody drug research and development and biotechnology.

Sorrento Resists M&A Frenzy

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The merger and acquisition merry-go-round is whirling again but Sorrento Therapeutics Inc. is not jumping on yet, having confirmed it has rejected an unsolicited buyout proposal from two biopharmaceutical companies.

The San Diego-based biotech, which has late-stage assets in non-opioid chronic pain and earlier programs in immuno-oncology (IO), has revealed that a non-binding term sheet proposal submitted by the two firms to acquire its shares for between $3.00 and $5.00 per share in cash landed on Sorrento's desk on 23 November. The lower bid represented a premium of around 88% over the company's share price on 22 November while the $5.00 offer would have been huge, valuing Sorrento at $710m.

An offer that would have tripled its market capitalization must have been tempting but after reviewing the proposal in consultation with advisors, Sorrento's board of directors declared that the offer significantly undervalued the firm and was not in the best interest of stockholders. The decision to unanimously reject the bid went down well with investors and Sorrento's share price closed up 94% to $3.11 on 25 November.

Sorrento noted that it was already in "active late-stage licensing and collaboration discussions with leading biopharmaceutical companies" for its IO products. The company claimed that "these pending transactions alone represent potential short- and long-term value creation significantly exceeding the current all-cash proposal."

The IO pipeline is headed by the firm's anti-CD38 chimeric antigen receptor-T cell (CAR-T) immunotherapy for the treatment of refractory or relapsed multiple myeloma. Sorrento has dosed five patients in a Phase I trial and a data readout is expected before the end of the year or the first quarter of 2020.

Other programs include an anti-carcinoembryonic antigen (CEA)-directed CAR-T in metastatic liver tumors, a CD38 antibody drug conjugate, and Seprehvir, Sorrento's oncolytic virus. The latter has been administered to over 100 patients in a variety of solid tumors including glioblastoma, mesothelioma, melanoma and head and neck cancer, as well as pediatric sarcomas and neuroblastomas.

PROMISING PAIN DRUG

Closer to the market is RTX, which is based on resiniferatoxin, a capsaicin analog that is 10,000 times hotter than the Carolina reaper, the world's hottest pepper. Sorrento's formulation is being evaluated for the treatment of pain due to osteoarthritis of the knee and a Phase Ib clinical trial presented in June this year showed rapid onset (less than a week) and extended pain relief out to 84 days.

Two Phase III trials are expected to start in early 2020 and each one is expected to enrol about 400 patients. Sorrento CEO Henri Ji noted that the firm has taken RTX from a preclinical investigational new drug application to registration trials in less than two years, adding that "because of the investigators' enthusiasm we have experienced for this ground-breaking non-opioid pain therapy in our initial trial, we expect the Phase III studies to move very quickly."

Speaking when the Phase Ib results were published, Ji said, "We want to be cautiously optimistic, as we are dealing with a small number of patients so far, but what we see is extremely promising. As we continue on this track, and provided all goes according to plan, RTX has the potential to be on the market by 2022."

ANALYSTS BACK REJECTION

Analysts at JMP Securities share Sorrento's enthusiasm and issued a note on 26 November saying "we agree that the offer substantially undervalued the company and the extensive pipeline in IO [and] pain." The firm also established a new business unit in April to focus on the market potential for its water soluble cannabidiol (CBD) formulation technology and has a presence in animal health.

The broker added, "We believe that the buyout offers do further validate the company, as large biopharma companies see value in Sorrento's pipeline. The current pace of M&A suggests possible additional competing offers may be possible." They added that RTX was a particularly attractive asset, noting that the company is seeking breakthrough designation from the US Food and Drug Administration for total knee arthroplasty (TKA) deferment. If all goes well, the analysts said, "We believe that insurers will likely insist that patients step through RTX before approving TKA for most of the 750,000 procedures performed annually."

JMP also pointed out that Sorrento owns 58% of "an interesting private company, Scilex Holding Co.." That company, which is also based in San Diego and is considering an initial public offering, sells the best-in-class topical pain product ZTLido (lidocaine) and has a spinal injection system called SP-102 in Phase III for lumbar radicular pain (sciatica). If approved, the analysts believe SP-102 "will likely replace the more than 10 million epidural steroid injections performed annually in the US."

Sorrento finished the third quarter with $35m and recently completed a $25m registered direct offering, providing it with $60m in total cash. JMP, which has a market outperform rating and a $21 price target on the stock, expects funds to last through the RTX and anti-CD38 data readouts.

The rejection by Sorrento of the unsolicited bid shows that biotech is a seller's market and serious amounts of cash need to be put on the table to force a buyout, as witnessed by Novartis AG plonking down $9.7bn to get hold of The Medicines Co.. A number of companies have seen their stock rise amid rumors they will be the next target, but for the time being, it seems Sorrento will not be tempted. *(Also see "Novartis To Pay $9.7bn For The Medicines Company" - Scrip, 24 Nov, 2019.)*

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Roche India Head On Way Out

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Lara Bezerra, managing director of Roche Products (India) Pvt. Ltd., is leaving the company after a short stint at the helm of the Swiss multinational's Indian operations.

Bezerra, who took charge in the country in late 2017, brought with her some less conventional management thinking and appeared keen to look at the Indian market through a different lens and beyond just the balance sheet. Interestingly, her current designation is Chief Purpose Officer.

Lara Bezerra

The decision, first reported in local media, will see the executive end her assignment at Roche India on 1 December, 2019. The Swiss firm gave no reason for Bezerra's departure and maintained that she had successfully led the organization with "passion and commitment" and shaped its culture.

Roche also noted that Bezerra took a very active role in "external engagement" and formed many close relationships with "key stakeholders and patient communities that are so close to her heart." *(Also see "Roche Primes New Push Via Cipla For Avastin, Actemra In India " - Scrip, 28 Feb, 2018.)*

"An announcement of the new India head will be made soon," Roche said.

Prior to her India stint, Bezerra was general manager of Roche in Venezuela at a time when the South American nation grappled with one of its worst economic crises. *(Also see "What's In Store For Roche's New India Boss?" - Scrip, 14 Nov, 2017.)*

'BUSINESS DELIVERABLES'

There's little clarity on what exactly prompted Bezerra's seemingly early departure and whether it is in any way connected with Roche's global restructuring plan, first disclosed last year. Asia had earlier seen some regional rationalization among other structural and personnel changes. *(Also see "Asia Begins To See Impact From Roche 'De-Siloing' " - Scrip, 18 Apr, 2019.)*

The local rumor mills are agog with speculation that the Indian operation's overall showing had not gone down well with some overseas executives and that there was an impression that, despite having great products, their potential was under-utilized in the field. "Finally, business deliverables matter and things appeared to be moving in a different tangent at the Indian operations," one industry expert told *Scrip*. But there is no official word on these matters and whether more executive changes may be in store.

It's also not clear what the leadership change could mean for the broad strategic thinking that Bezerra espoused at Roche India and whether plans may now be re-calibrated.

Bezerra, in a previous interview with *Scrip*, had highlighted a thrust towards improving patient numbers; revenue build-up, she indicated at the time, would follow.

"If we don't think [about] what is important – the patients – the revenues will not come. And this is the tricky part. If you think revenue, you will look short-term and only focus on affordability and you will not take the big jump that is really needed to move the needle here in India," Bezerra said at the time. *(Also see "Roche India Mandate 'Completely Different' Says New Head Bezzera" - Scrip, 8 Apr, 2018.)*

ENTHUSED BY HEALTHCARE SCALE-UP EFFORTS?

Bezerra also appeared enthused by India's ambitious National Health Protection Scheme (NHPS), dubbed Modicare, and the efforts by some Indian states to sharpen their focus on improving healthcare. The NHPS expects to provide for 100 million poor and vulnerable families with health cover of up to INR500,000 ($6,983) each annually for secondary and tertiary care hospitalization and is expected to facilitate significant pharma market expansion.

In one of her previous online posts, Bezerra had referred to India's national health program and how the country aimed to utilize this scheme to implement a National Health Stack (NHS) that might have the potential to "align all actual technology in the country", state-wise or centrally. "Both public and private sector can benefit," Bezerra said in the post.

The NHS envisages a centralized health record for all citizens of the country in order to streamline health information and facilitate its effective management. It aims to employ the latest technology including big data analytics and artificial intelligence and create a unified health identity for citizens as they navigate services across primary, secondary, tertiary and also public and private care.

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Who's In And Who's Out In China's Largest Reimbursed Drug List Revamp?

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Some globally well-known drugs are now being offered at prices affordable to the common public in China, precisely what the country's Medical Insurance and Support Administration had in mind when announcing an updated National Reimbursement Drug List (NRDL) on 28 November.

Out of 119 novel drugs that newly qualified for the coverage, 70 were eventually added to the list, meaning they are reimbursed by the national medical insurance program. The cost of the addition was a 60.7% average price reduction across the board but the steepest cuts ranged up to more than 85% for hepatitis C regimens. 22 cancer drugs were also included and these together with anti-diabetics also saw price reductions of more than 65%.

Meanwhile, 27 out of an existing 31 drugs that were subject to price re-negotiations saw their prices cut further by 26.4% on average.

Other than these steep price reductions and the other newer drugs, seven others for rare conditions were also included in the list, 14 for chronic diseases and four pediatric drugs.

After the latest revamp, the largest change ever in the NRDL's history, the new list will include 2,709 drugs, with 218 new additions and 154 deletions compared to the 2017 revision. The new list will take effect from 2020.

CANCER DRUGS DOMINATE

Oncology once again dominated the changes to the NRDL, with multinationals Roche, AstraZeneca PLC and Novartis AG securing gains for their novel therapies, along with Hutchison China MediTech Ltd., Jiangsu Hengrui Medicine Co. Ltd. and Chiatai Tianqing.

Roche has Perjeta (pertuzumab) and Alecensa (alectinib) newly covered, AZ's PARP inhibitor Lynparza (olaparib) and Novartis's JAK inhibitor Jakafi (ruxolitinib) were included, as were Chi-Med's Elunate (fruquintinib) and Hengrui's Iruini (pyritinib).

Novartis seemingly has the most new coverage going beyond oncology, as the Swiss group's Entresto (sacubitril/valsartan) and Lucentis (ranibizumab) also gained NRDL inclusion this time.

Notably, Eisai Co. Ltd.'s Lenvima (lenvatinib) was not included despite being approved in 2018 and indicated for hepatocellular carcinoma, one of the most prevalent cancer types in China.

SOLE PD-1 GETS COVERED

Despite previous reports suggesting that Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab) would be in the running for inclusion, the finalized list shows that Innovent Biologics Inc.'s Tyvyt (sintilimab) was the only PD-1-targeting drug to get coverage.

Jointly developed by Innovent and Lilly Research Laboratories, the product obtained approval on 24 December, 2018, meaning it barely qualified for the update, which included drugs approved before 31 December that year. Competing in a crowded area in which two multinationals - (Bristol-Myers Squibb Co. and Merck - and three domestic makers have rival products, the decision to cut prices to ensure inclusion and get coverage looked to be a natural one to the Suzhou-based firm.

An additional consideration for inclusion is a product's indication, analysts say. Tyvyt is approved for Hodgkin's lymphoma, meaning it competes head-on with Jiangsu Hengrui's PD-1 AiRuiKa (camrelizumab) and BeiGene Ltd.'s tislelizumab, which is pending approval.

Hengrui's product did not participate in the NRDL negotiations due to its later approval (this May), while another domestic anti-PD-1 drug, Tuoyi (toripalimab) from Junshi is indicated for melanoma, which has a relatively small patient population in China.

Junshi has already priced its product lower than all other competitors and thus has little room for further cuts, giving Innovent the chance to get the first NRDL coverage for a PD-1 molecule in China. The reimbursement price for Tyvyt is CNY2,843 ($404.40) per 10mL/100mg vial.

HCV DRUGS THE POSTER CHILD?

The steepest cuts in relation to the updated list came for three hepatitis C drugs, Gilead Sciences Inc.'s Epclusa (sofosbuvir – velpatasvir) and Harvoni (ledipasvir – sofosbuvir) and Merck's Zepatier (elbasvir/grazoprevir), for which prices were cut by 85% on average.

The steep reductions were due to rigorous negotiations, noted Xianjun Xiong, director of Medicines Management and Services at the National Healthcare Security Administration, in a 28 November press briefing.

The NRDL negotiation mechanism allows only two drug makers offering the lowest costs covering a whole treatment cycle to compete, but then guarantees them two years of supply to the scheme. That tactic has made suppliers slash prices aggressively, noted Xiong.

HCV regimens are likely the poster child for this policy of coverage in exchange for price concessions, in which companies hope the expanded coverage and promised bulk volumes will offset the price reductions.

Hepatitis C is also an area with high growth and Gilead has been dominating it with its two big-selling drugs Sovaldi (sofosbuvir) and Epclusa.

In other areas, three SGLT-2 inhibitors for diabetes were covered by the updated list - AZ's Farxiga (dapagliflozin), Boehringer Ingelheim International GmbH's Jardiance (empagliflozin) and Janssen Pharmaceutical Cos.'s Invokana (canagliflozin).

Also included were the GLP-1 receptor agonists Sanofi's Adlyxin (lixisenatide) and Lilly's Byetta (exenatide).

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Global Blood Therapeutics' Oxbryta Approved Broadly For Sickle Cell Disease

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Global Blood Therapeutics Inc. will be launching its first commercial drug, Oxbryta (voxelotor), for the treatment of sickle cell disease after securing FDA approval on 25 November. The drug will be available in two weeks, the company said.

Oxbryta is the second drug approved by the US Food and Drug Administration for sickle cell disease in just over one week, a landmark moment for the devastating blood disorder after years of disappointments and lack of investment on the part of pharma.

Novartis AG' Adakveo (crizanlizumab) was approved by the FDA on 15 November, but the two drugs work differently and carry different indications. Adakveo is approved to reduce vaso-occlusive crises (VOCs) in sickle cell disease patients. Those are the terrible pain crises that can drive patients into the hospital, but for which there are limited treatment options. *(Also see "FDA Approval For Novartis's Sickle Cell Treatment Adakveo" - Scrip, 18 Nov, 2019.)*

GBT's Oxbryta, on the other hand, was approved with a broad label for the treatment of sickle cell disease in adults and pediatric patients 12 and older. It works by inhibiting sickle hemoglobin polymerization and could be the first drug to address the underlying cause of sickle cell disease.

Oxbryta will carry a six-figure price tag, however, that the company says reflects its potential to modify the course of the disease. The wholesale acquisition cost will be $10,417 per month, or $125,000 per year. The net price of the drug for about 65% of US patients will be lower, around $8,000 per month, GBT said. The company vowed not to raise the price of the drug for three years.

"We considered lot of factors, and this included the cost and burden of the disease, the prevalence of the condition, the direct and indirect cost of care, and the value and the impact we feel Oxbryta, as an innovative treatment, in the context of currently available options, has to reduce health care costs," Chief Commercial Officer David Johnson said during a same-day conference call.

"We believe strongly the value Oxbryta brings to the sickle cell community has hit that balance, and that is the balance of a transformative medicine like Oxbrtya, not only the hemolysis that is on the label today, but what we can show over time," he added.

The drug is an oral small molecule but will be priced higher than Novartis' Adakveo, a biologic; Novartis said Adakveo will cost most patients $84,852 to $113,136 per year in the US.

Because Adakveo and Oxbryta work differently and address different problems associated with sickle cell disease, it's expected that both drugs will carve out a niche in the market and they could potentially be used together. *(Also see "Sickle Cell Disease Market Snapshot: "The Time Has Come" " - Scrip, 31 Oct, 2019.)* Oxbryta is an oral drug, while Adakveo, a monoclonal antibody targeting p-selectin, is an injected biologic.

Oxbryta was approved based on the results of the Phase III HOPE study, which showed an increase in hemoglobin response rate in patients who received the therapy, but GBT believes it could address lots of other problems associated with the disease,

A new drug is approved for sickle cell disease.

including strokes, organ damage and pain crises, though that is yet to be proven in clinical trials. In the HOPE study, Oxbryta did not statistically improve VOCs, though it did so numerically.

Sickle cell disease is an inherited blood disorder that mostly affects people of African or Hispanic descent. There are only about 100,000 patients with sickle cell disease in the US, but millions of patients globally, with the majority being in Africa. The chronic disease is caused by a genetic mutation in a single protein inside red blood cells responsible for transporting oxygen, which results in sticky sickle-shaped red blood cells. The disease results in painful acute attacks known as VOCs as well as organ damage, including to the brain, lungs and kidneys, and eventually leads to early death.

The approval of Oxbryta was based on the HOPE trial, which enrolled 274 patients with sickle cell disease. Of the patients receiving the drug, 51.1% achieved a greater than 1g/dL increase in hemoglobin compared with 6.5% receiving placebo. *(Also see "Global Blood Therapeutics' Voxelotor On Track For 2020 Sickle Cell Shakeup " - Scrip, 5 Sep, 2019.)* The hemoglobin improvement endpoint is a novel one for sickle cell disease, where drug companies have typically focused more on the pain episodes as a primary endpoint in clinical studies.

The company and the FDA have agreed on a confirmatory trial endpoint that would rely on transcranial doppler flow to demonstrate stroke risk reduction in pediatric patients. GBT said it is on track to initiate the trial by the end of the year and will enroll roughly 220 patients. The company is also planning to conduct several other post-approval studies to evaluate the efficacy of Oxbryta on other endpoints.

The FDA approval is also a landmark moment for GBT because Oxbryta is the company's first FDA-approved medicine, coming after a rapid development path, just five years after the investigational new drug application was filed and two months after the new drug application was accepted by FDA. GBT is the first company focused specifically on sickle cell disease to get a drug to market.

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Celltrion Lays Out Europe Launch Plans, Strategy Following Remsima SC Approval

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Celltrion Inc. has received European Medicines Agency (EMA) approval for the world's first subcutaneous (SC) biosimilar version of infliximab, Remsima SC, giving the South Korean company another foothold to evolve into a truly global enterprise, as it laid out its commercial plans and strategy for the roll-out in Europe.

The formal regulatory nod came after the company received a positive opinion in the EU in mid-September for its approval filing made a year ago. Remsima SC has passed through the marketing authorization extension route, given the lack of a formal pathway for "biobetters" in Europe. *(Also see "Celltrion Pushes 'Biobetters' Concept With Remsima SC" - Generics Bulletin, 15 Nov, 2019.)*

The latest approval for the SC formulation covers only rheumatoid arthritis, but Celltrion plans to get approvals for the entire set of current indications for its intravenous Remsima product, which include inflammatory bowel disease and psoriasis, by mid-2020. Therefore, it expects Remsima SC to accelerate penetration and gain momentum in the European market after that.

The company said that after it completes patent registrations in 130 countries, it expects to have market exclusivity of the product for the next 20 years.

'PRIME SIMILAR' POSITIONING STRATEGY

Celltrion expects Remsima SC to make a large contribution to enhancing its profitability as it will be sold at a higher price than current original first-line treatments such as Humira (adalimumab), Enbrel (etanercept) and Remicade (infliximab), but will be priced competitively versus other second-line treatments to grab market share.

The firm believes Remsima SC can generate total estimated sales of KRW10tn ($8.5bn) in a global anti-TNF-alpha inhibitor market it values at KRW50tn. Celltrion sees patients who need to move on to second-line therapy because they

do not respond adequately to first-line TNF-alpha inhibitors as the key target for Remsima SC. Availability in dual formulations is also expected to help take share from other biosimilars.

About 25% of patients administered TNF-alpha inhibitors (Humira, Enbrel and Remicade) in the first line develop resistance and have to move on to second-line treatments such as Orencia (abatacept), Actemra (tocilizumab), Entyvio (vedolizumab) and Stelara (ustekinumab), said Celltrion, adding these can cost about $20,000 annually.

Celltrion is targeting these patients for Remsima SC before they move on to second-line drugs and also expects to absorb some patients prescribed infliximab products, as well as Humira and Enbrel, thanks to Remsima SC's efficacy and administration convenience.

CELLTRION HEALTHCARE TO SELL DIRECTLY IN EU

The company believes it has demonstrated sufficient evidence for Remsima SC to be positioned as a "prime similar", for example by presenting clinical and comparative data at international conferences such as European League Against Rheumatism and United European Gastroenterology Week, and confirming positive responses to the product from local physicians.

Celltrion Healthcare, which handles international distribution and marketing activities for Celltrion, plans to directly sell Remsima SC in Europe through its already established 14 units and branches in the region. After the February 2020 launch in Germany, it plans to sell the product in the UK and Netherlands in March and then the entire European market by the end of 2020.

To step up its marketing capability in Europe, it plans to hire around 300 commercial staff by the end of next year.

A US launch is planned in 2022, through which Celltrion will "challenge the global TNF-alpha market," the company said.

DIFFERENTIATED MARKETING STRATEGY

In addition, Celltrion Healthcare plans to lead the TNF-alpha inhibitor market and strengthen the loyalty of physicians and patients by providing support services tailored to those who administer Remsima in its IV and SC form. These services will include a nurse consultancy program in which nurses will visit patients' homes and provide information and product educations, as well as a monitoring kit to enable patients to keep track of disease status and treatment efficacy, as well as a mobile application to enable two-way communication between patients and physicians.

Celltrion's biosimilar business in Europe is already growing steadily. As of the second quarter, Remsima IV accounted for 59% of the market, while Truxima (rituximab biosimilar) and Herzuma (trastuzumab biosimilar) held a 38% and 15% market share, respectively.

As part of its ongoing strategy for the SC formulation, Celltrion Healthcare plans to continue to attend global conferences and hold product briefings to increase physicians' interest and what it terms the "credibility" of prescriptions. It also plans to hold advisory board meetings for physicians and expand investigator-initiated trials to further shore up medical interest in Remsima SC.

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Rapid US FDA Review For Roche's SMA Contender

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Roche has been granted a priority review in the US for risdiplam, which could challenge or be used alongside Biogen's Spinraza and Novartis' Zolgensma in spinal muscular atrophy (SMA), thanks especially to its oral formulation.

The US Food and Drug Administration is expected to make a decision by 24 May 2020, and a rapid approval would help Roche compete with the two established treatments for the rare condition.

Some indication of how the market might pan out in this three-way competition is given in a survey of 30 physicians in US and EU currently treating SMA patients conducted by analysts Jefferies earlier this year, and provides good news for all the competitors.

Its three conclusions were that Zolgensma is likely to be used for the majority of new SMA patients; secondly that most doctors would consider combination therapy; and finally that oral drugs were seen as an appealing option.

Comments from Roche earlier this year backed up this view on combination therapy, with CEO Severin Schwan saying risdiplam could be a "very important complementary option to other therapies."

That led Jefferies to conclude that risdiplam could hit peak global revenues of $600m, with consensus estimates for Zolgensma (onasemnogene abeparvovecxioi) around $2bn.

This would still leave it the poor relation to Spinraza (nusinersen) and Zolgensma, given the former's established market lead (earning $1.7bn in 2018) and the more profound clinical benefit expected from the latter in the long term, as it replaces the defective or missing SMN1 gene.

However there are likely to be some twists in the tale, with Novartis recently hitting a problem with its intrathecal (IT) injection plans.

Novartis AG gained US approval for Zolgensma in May in infants under two years of age with type 1 SMA (the most common and severe variant).

It is looking to expand into older age groups with the less severe SMA types 2 and 3 using IT administration, but its trial in this formulation was recently suspended by the FDA because of safety concerns based on preclinical data.

While Novartis has confined itself to these infant patients in the first instance, Roche is pursuing a broader approval at the first time of asking, which would cover all ages from new born infants to 60 year olds.

This would also include patients previously treated with other SMA therapies.

Risdiplam is a survival motor neuron-2 (SMN-2) splicing modifier for SMA, designed to increase and sustain SMN protein levels in the central nervous system and peripheral tissues of the body.

ROCHE'S PIVOTAL STUDIES

It is uncertain whether the FDA will grant approval for risdiplam in type 1 patients on this occasion, as Roche is only providing efficacy data for type 2 and 3 patients.

Roche's submission to the FDA includes data from two studies, FIREFISH (in SMA type 1 and SUNFISH (in SMA types 2 and 3). However the filing only includes FIREFISH Part 1, in which efficacy is only "an exploratory endpoint" alongside safety data. The open-label FIREFISH trial is expected to produce outcomes data from its single-arm 24-month Part 2 trial in November 2023. That means it may not be able to challenge Zolgensma and Spinraza in this key group until then, although the FDA may well grant it conditional approval given the need for treatment options.

The company has supplied efficacy data from its double-blind, placebo-controlled pivotal SUNFISH trial in children and young adults (2-25 years old) with Type 2 or 3 SMA. Roche announced on 11 November that it had met its primary endpoint of change from baseline in the motor function measure 32 (MFM-32) scale, but details will not be unveiled until a forthcoming medical congress.

No safety problems leading to patients dropping out of risdiplam trials have been recorded so far – a good safety profile which will also make it attractive compared to its more established rivals.

Two further trials, JEWELFISH, in SMA patients previously treated with the other agents, and RAINBOWFISH in newborn infants not yet displaying symptoms, are both current recruiting.

Nonetheless, Roche is still expected to trail its two rivals, especially Zolgensma, which has enjoyed a better-than-expected launch.

The drug's record-breaking high price of $2.1m has caused a stir, but Novartis' argument that it will save money compared to a lifetime's treatment of Spinraza has been well received so far. It has exceeded analysts' expectations by generating $160m in revenue in Q3, its first few months on the market, treating 100 patients.

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'Serial Killer' CAR-T Could Help Autolus Bounce Back

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Autolus Ltd. is looking to get back on track after numerous setbacks in its goal to produce the next generation of CAR-T products.

The UK-based biotech's problems have been reflected in a share price which has lost nearly two-thirds of its value since January.

This has been caused by setbacks to its pipeline, intense competition in the CAR-T space (leading to abandonment of multiple myeloma candidate AUTO2) and major delays to its cell therapy manufacturing plans.

On top of this, confidence in the company has also been hit by the fall of Neil Woodward, one of its key investors. But CEO Christian Itin and lead investor,

London-based health venture capital firm Syncona, still believe that Autolus can be a player in the next generation of T-cell based therapies.

The company will be at the American Society of Hematology (ASH) congress in Orlando, Florida (7-10 December) where it hopes several key data presentations will revive investor belief in its pipeline.

This year's ASH will feature lots of CAR-T contenders, however, and Autolus's data will have to shine to attract attention.

A CAR-T FOR ADULT ALL

Autolus's lead product is AUTO1, and is designed to improve upon current treatments for acute lymphoblastic leukemia (ALL) in both children and adults.

Novartis' Kymriah (tisagenlecleucel) is the pioneer CAR-T in pediatric ALL, and has produced remarkable results in relapsed/refractory (R/R) patients, with trial data showing two-thirds of treated patients likely to survive for two years after treatment.

Itin presented at the Jefferies investor conference in London on 20 November, and gave an upbeat overview of Autolus' extensive preclinical and Phase I pipeline of CAR-Ts and other novel T-cell therapies.

Autolus believes it can improve on the durability of response with its next generation CAR-T AUTO1, which is designed to disengage from cancer cells more easily and then move on to the next target, making it a "serial killer" T-cell therapy.

The biggest advantage of this so-called 'fast off' mechanism is that it does not produce the high levels of severe cytokine release syndrome (CRS), a major safety issue for nearly half of children taking Kymriah.

But it is the less common adult ALL, for which there are no CAR-T therapies currently approved, that Autolus has made its priority.

There is a small population of just 3,000 adult ALL patients in the US and major European markets. These adult patients are generally less likely to tolerate toxicity compared to pediatric ALL patients, making a CAR-T with fewer CRS adverse events favorable.

The current standard therapy for adult ALL is Amgen's Blincyto (blinatumomab), and Autolus's early studies show its therapy achieved a superior complete response rate – 83% to Blincyto's 42%.

AUTO1 vs. Kymriah and Blincyto in ALL

	KYMRIAH - PALL	AUTO1 - PALL	BLINCYTO AALL	AUTO1 - AALL
Patient Numbers	75	14	271	13
Complete Response Rate	81%	86%	42%	83%
Event free survival (EFS)	EFS 12m: 50%	EFS 12m 52%	EFS 6m: 31%	TBD
CRS ≥ Grade 3	47%	0%	3%	0%
Neurotox ≥ Grade 3	13%	7%	13%	8%

The biggest advantage of this so-called 'fast off' mechanism is that it does not produce high levels of severe cytokine release syndrome.

Investigators will present follow-up data from the Phase I trial, including further safety and efficacy at ASH on Saturday 7 December.

For pediatric ALL, AUTO1 achieved a complete response (CR) rate and event-free survival (EFS) slightly better than Kymriah.

Most significantly, it produced no instances of severe CRS, compared with Kymriah's 47%. Autolus's dataset for AUTO1 is far smaller than that of Novartis however, with 14 and 75 patients trialed respectively.

The ASH abstract shows that in adult ALL, AUTO1 clearly outperforms Blincyto, achieving 83% compared with its established rival's 42%. This would make Autolus's product twice as active as the current standard of care with a similar safety profile.

Autolus is gearing up to begin a pivotal study with around 100 patients in this population, a clinical trial application filed in the UK in November and US IND to be filed in Q1 2020.

The company says this would put it on track to file a biologics license application (BLA) with the US Food and Drug Administration in H2 2021.

BISPECIFIC CAR-TS

However there are several other companies targeting the adult ALL space, including Gilead's Kite and Pfizer, which presented encouraging data on a CD19-targeting KTE-X19 at ASCO earlier this year; this product is now in Phase II trials.

The field is now moving on to bispecific CAR-Ts in order to overcome the limitations of CD19 targeting Kymriah and Yescarta (axicabtagene ciloleucel) which can stop working in patients because of the loss of this CD19 antigen in target cancer cells.

Kite and Pfizer will be presenting Phase I data from their dual CD19 and CD22 targeting agent in R/R pediatric and adult ALL patients at ASH. Its abstract data suggest promising efficacy, and CRS cases limited to milder grades 1 and 2.

Autolus has its own CD19+CD22 targeting bispecific CAR-Ts in development, and its NG or next generation version of AUTO1 is set to enter Phase I in the first half of next year. AUTO3 uses the same mechanism, and data from a Phase I trials in ALL and a Phase I/II in DLBCL (the lucrative therapy area currently led by Yescarta) will also be presented in Orlando.

While the company currently has no big pharma partners in any of its programs, it is not clear if it can deliver on its ambitions across multiple targets and novel T-cell platforms. This may well change in the next few months, and Autolus could attract partners if and when it accrues some compelling proof of concept data.

The company has not given up on multiple myeloma, meanwhile, one of the most hotly contested therapy areas. It was forced to abandon its AUTO2 candidate because of fears it could not compete with close-to-market BCMA-targeting contenders such as BMS/Celgene/bluebird's bb2121, but Autolus has a new myeloma candidate in development with an as-yet undisclosed target, which it says will begin Phase I trials in the second half of 2020.

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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, 22–28 NOVEMBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	TauRx Therapeutics Ltd.	hydromethylthionine	Alzheimer's Disease	Journal of Alzheimer's Disease, 26 Nov, 2019	0	44
Phase III Updated Results	Tocagen, Inc.	Toca 511, gene therapy	Glioma, High Grade	Toca 5 (w/lomustine); Mixed Results	0	22
Phase III Updated Results	Roche Holding AG	atezolizumab/bevacizumab	Hepatocellular Cancer, First Line	IMbrave150; Improved OS And PFS	5	46
Phase III Updated Results	Takeda Pharmaceutical Co	TAK-003, vaccine	Dengue Fever	TIDES; Positive 18-month Data		63
Phase III Updated Results	Poxel SA	imeglimin/insulin	Diabetes Type 2	TIMES 3; Met Primary Endpoint	0	22
Phase III Top-Line Results	ChemoCentryx/Vifor	avacopan	ANCA-Associated Vasculitis	ADVOCATE; Positive Data	9	70
Phase III Trial Clinical Hold	CymaBay Therapeutics, Inc.	seladelpar	Primary Biliary Cholangitis, Hepatic Fibrosis	Atypical Histologica l Findings	0	66
Phase III Trial Initiation	Alnylam/Sanofi	vutrisiran	Transthyretin Amyloid Cardiomyopathy	HELIOS-B; Placebo Controlled Trial	0	64
Phase III Trial Initiation	Akcea Therapeutics/Ionis Pharma	AKCEA-TTR-LRx	HATTR Amyloidosis With Polyneuropathy	NEURO-TTRansform; An Antisense Molecule	38	62

Source: Biomedtracker | Informa, 2019

Acadia Revives Nuplazid's Chances In Schizophrenia With Negative Symptom Data

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Acadia Pharmaceuticals Inc. has been striving for several years to build out the label for its Parkinson's psychosis drug Nuplazid (pimavanserin), and things took a turn for the better on 25 November when the company reported success in a 403-patient Phase II study of schizophrenia patients with negative symptoms.

The data follow a major setback in June, when the drug failed a Phase III study testing it for adjuvant treatment of refractory schizophrenia. Even then, however, the San Diego firm reported positive signs from the Phase III ENHANCE study in negative symptoms, which include social withdrawal, lack of emotion, restricted speech and blunted affect. There are no approved drugs for schizophrenia's negative symptoms, although there are multiple approved drugs for hallucinations and delusions, which are termed positive symptoms of the disease.

The 26-week ADVANCE study in patients whose positive symptoms of schizophrenia are controlled on existing antipsychotic therapy showed a statistically significant improvement from baseline compared to placebo on the primary endpoint, the Negative Symptom Assessment-16 (NSA-16) score. Randomized 1:1, the trial showed a 10.4-point change in NSA-16 score for patients on study drug, compared to an 8.5-point improvement for placebo (p=0.043, effect size=0.21).

Acadia president Serge Stankovich told a same-day investor call that that magnitude of effect compared to placebo is considered clinically relevant, particularly for a patient base with no approved therapy. "We believe an effect size of anything above 0.2 on the NSA is a meaningful improvement, particularly in the context of this indication where nothing is approved or available," he said. "And that's the feedback that we have been receiving and the overall opinion."

The company also stressed that in patients whose dose was increased during the treatment period from the starting dose of 20mg to a maximum of 34mg, the separation from placebo was greater. These patients comprised nearly 54% of the enrollment, with an 11.6-point improvement for those receiving pimavanserin and an 8.5-point improvement for the control group (p=0.0065; effect size=0.34).

ACADIA TO MOVE FORWARD WITH 34MG DOSE

The study employed a flexible dosing regimen under which all patients started on 20mg daily of pimavanserin, with the clinician then deciding whether to maintain that dose or adjust upward to 34mg or downward to 10mg. While 107 treatment-arm patients (53.8%) were increased to 34mg, 44.7% stayed at 20mg and 1.5% were reduced to 10mg.

Stankovich noted that Acadia has decided to use the 34mg dose in a pivotal study it plans to initiate during the first half of 2020, with the greater effect size giving it confidence of success with that dose.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Jonathan Biller	Agios Pharmaceuticals	Chief Legal Officer	Celgene Corp	Executive Vice President, General Counsel	3-Dec-19
Elizabeth Radcliffe	Arrakis Therapeutics	Vice President, Finance and Strategy	Angios Pharmaceuticals	Vice President, Financial Planning and Analysis	19-Nov-19
Laurent Chardonnet	Axcella Health Inc	Chief Financial Officer	Incyte Corp	Vice President, Alliances	25-Nov-19
Roberto Camerini	Cosmo Pharmaceuticals NV	Chief Scientific Officer	Alf Wassermann SPA	Director, Preclinical and Clinical Research and Development	1-Jan-20
Paul Woodard	Immune-Onc Therapeutics Inc	Chief Medical Officer	Bellicum Pharmaceuticals Inc	Senior Vice President, Clinical and Medical Affairs	19-Nov-19
Jeroen Weites	JSC Olainfarm	Chief Executive Officer and Chairman	Sanofi Bulgaria	General Manager, Global Healthcare	28-Nov-19

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

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