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Pfizer's Bourla: "I Think We Forgot What It Looks Like To Grow"

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Pfizer Inc. CEO Albert Bourla took over the top leadership spot from Ian Read a year ago, but has quickly executed on big changes poised to make Pfizer significantly smaller and faster growing. The chief exec looked back at his first year of leadership, and the state of the company, from the stage of the Forbes Healthcare Summit in New York City.

"I think we forgot what it looks like to grow," Bourla told attendees during a presentation on 5 December. "Growth culture is a very different culture [versus] when you need to just control costs."

Pfizer is being reshaped through the spinout of its consumer health care and Upjohn established products business, balanced with small to mid-sized deals to add to the innovative pharmaceutical pipeline. The company announced in July it will merge the Upjohn business with Mylan NV to form a new generic drug company to be called Viatris GMBH.

The resulting Pfizer will be significantly smaller, with a 2020 annual revenue base of around $40bn from a 2018 base of $53.65bn, but growing at about 6%.

Bourla said he is confident the company will maintain a 6% growth rate through 2025 at least because the company isn't facing big patent losses during that timeframe. Right now, Pfizer is cycling through the loss of the blockbuster Lyrica, which is weighing on 2019 revenues.

"We have a unique window of opportunity to get it right," Bourla said. That timeline is about six or seven years because after that, more patent losses will be coming. His primary goal, he said, is to sustain the solid growth beyond 2027, relying on pipeline success and business development.

"In the next two years, we need to see how the pipeline is delivering," he said.

Bourla has been outspoken that when it comes to business development, he doesn't see a mega-merger on the horizon. Instead, he said he is looking to bring in mid-stage clinical development assets to complement the internal pipeline.

It sounds like investors can expect the company to be active on the business development front within those guardrails. "I want to double it," he said of the pipeline, which includes 92 projects right now. "And, we are going to double it by bringing in a lot of innovation to complement what we distribute."

The company is focusing business development on six core therapeutic areas as well, but Bourla indicated the company will be actively building out those areas both through internal investment and external collaboration. "We're going to be active because Pfizer is a very big plane and it cannot fly with one engine," he said.

Bourla highlighted Pfizer's recent acquisition of the cancer specialist Array BioPharma for $11.4bn as an example of the kinds of deals the company will be pursuing. "When I saw the royalties they are collecting from 10 different companies, I realized this is a company that has produced. Why don't we get them?"

While Pfizer is executing on business development, Bourla said another big priority for him in the near-term is changing the culture at Pfizer, a common refrain among the industry's new big pharma leaders.

Bourla said he is striving to create a youthful, patient-centric, risk-taking environment at Pfizer, so that the employees feel it is a "company that thinks big, that has courage."

But he said he is only building on the groundwork laid by former CEO Read.

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from the editor

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For the last issue of the year, I'd like to highlight just two of the many inspiring people who are making a difference to human health through drug development.

Jane Osbourn OBE was announced last week as the winner of the 2019 Scrip Lifetime Achievement Award. Her career in antibody engineering has spanned academia and industry and contributed to the development of Humira and Benlysta. In her moving acceptance speech, Osbourn talked about how a sense of responsibility towards patients drove her and her team on, and also about the importance of team work, diversity, risk taking and openness. But her best advice was "be generous" – with ideas, time and support for others.

One person who has been incredibly generous is Nicola Curtin, a professor at Newcastle University, UK. Her work contributed to the development of the PARP inhibitor Rubraca, which was approved for ovarian cancer in the US in 2016 and in the EU in 2018.

Not content with saving the lives of women with ovarian cancer, Curtin decided that it was "wrong for me to benefit from this financially," and with her share of the royalties from the drug she set up the Curtin PARP (Passionate About Realising your Potential) Fund, donating £865,000 to help disadvantaged people overcome barriers to employment or education. "I'm proud that this research will change lives, and I have everything I need in life," she explained.

Both Curtin and Osbourn are shining examples in our industry, which has the great privilege of helping humanity and making money in the process.

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Interview: Double Delight For ImmuPharma's Dimitriou

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ImmuPharma PLC CEO Dimitri Dimitriou had an excellent day on 28 November as his daughter got married and the UK biotech signed a deal for Lupuzor with the US's Avion Pharmaceuticals LLC that has breathed new life into the prospects for the investigational lupus drug.

The pact will see Avion pay for a new Phase III trial up to $25m for Lupuzor (forigerimod), ImmuPharma's first-in class autophagy immunomodulator which has been on a less than smooth development path. That path got particularly bumpy In April last year when late-stage data showed that while Lupuzor plus standard of care (SOC), such as steroids, anti-malarials and methotrexate, was more effective than placebo plus SOC (52.5% versus 44.6%), the high response rate in the latter group meant the primary endpoint of statistical significance was not reached.

Dimitriou said it was important to point out that it was probably the SOC effect rather than placebo that led to the higher than expected response rate and missing statistical significance. He added that in hindsight, setting that endpoint and not targeting only patients in the active state of the disease was unfortunate "and while we took a big hit, we knew that in the right patients, the drug worked."

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Astellas To Pay $3bn For Gene Therapy Company Audentes

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Astellas Pharma Inc. is to acquire Audentes Therapeutics for $3bn, in a transaction that confirms the abiding attraction of gene therapy companies for big pharma companies looking to update their pipelines.

The Japanese big pharma company has agreed with the San Francisco-based company's board to pay $60.00 per share in cash to acquire it in full, representing more than double its closing market capitalisation.

The high price Astellas has paid will undoubtedly raise eyebrows among analysts and investors, who over the course of 2019 have grown more skeptical about the long term commercial value of these first generation cell and gene therapy platforms.

However this has helped to drive down the value of gene therapy companies in 2019, Audentes included, which has seen its share price fall 30% since August.

This means Astellas has been able to bag itself a bargain relative to valuations earlier this year, and must now show how it can help develop and commercialise Audentes Therapeutics Inc.' platform and pipeline.

Audentes is focused on developing treatments for serious rare neuromuscular diseases using its AAV gene therapy technology platform.

Its lead candidate is AT132, a gene therapy being developed to treat XLMTM, a serious, life-threatening, rare neuromuscular disease which causes extreme muscle weakness. The inherited condition affects male infants and results in respiratory failure and early death. The therapy has shown promise in interim results from a Phase I/II trial.

Analysts at Jefferies were positive on the move, but noted that only 40 boys are likely to be born with XLMTM every year in the US, and calculated therefore that US annual revenues might reach just $80m.

On that basis, Astellas will be looking to the potential of Audentes' work across three modalities – gene replacement, vectorized exon skipping, and vectorized RNA knockdown – to provide much broader opportunities. Programs already in Audentes' preclinical and discovery pipeline include Pompe disease, Duchenne muscular dystrophy and Mytonic dystrophy.

"Recent scientific and technological advances in genetic medicine have advanced the potential to deliver unprecedented and sustained value to patients, and even to curing diseases with a single intervention," said Kenji Yasukawa, president and CEO, Astellas.

He added: "Audentes has developed a robust pipeline of promising product candidates which are complementary to our existing pipeline, including its lead program AT132 for the treatment of X-Linked Myotubular Myopathy (XLMTM). By joining together with Audentes' talented team, we are establishing a leading position in the field of gene therapy with the goal of addressing the unmet needs of patients living with serious, rare diseases."

The value of the acquisition comes close to the $4.3bn Roche has offered for another gene therapy company, Spark Therapeutics.

One key difference between that transaction (still awaiting regulatory sign off) and this latest deal is that Spark already had its first gene therapy on the market at the time of the acquisition, rare eye disease gene therapy Luxturna.

The deal isn't Astellas' first foray into gene therapy, Last year it spent $109m to buy out UK ophthalmic gene therapy company Quethera, and also has a licensing deal with fellow Japanese firm Clino in retinitis pigmentosa, and a research alliance with Harvard Medical School.

Other notable transactions in the field include Novartis AG' $8.7bn acquisiton of AveXis in 2018, which brought with it the now-launched Zolgensma, and the much smaller $800m buy-out of UK-based gene therapy company Nightstar by Biogen in March 2019.

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Novartis Enters 'Transformational' Cloud Computing Pact With Amazon

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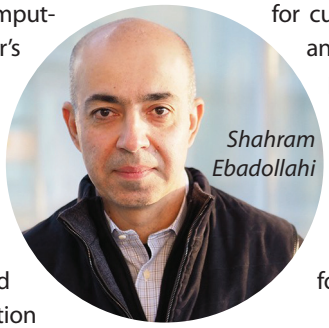
Novartis AG has turned to Amazon's Cloud computing expertise to hone the Swiss drug maker's pharmaceutical manufacturing, supply chain, and delivery operations by making them more efficient and real-time.



Shahram Ebadollahi

The head of data science and AI at Novartis told *Scrip* the multiyear collaboration with Amazon Web Services (AWS), announced on 4 December, will build an enterprise-wide, global data and analytics platform designed to form the foundation for custom, cloud-based solutions that enhance agility and cost efficiencies across the drug maker's business processes and systems. The partnership will see the creation of command "Insight Centers" to provide real-time visibility across Novartis's global manufacturing operations and distribution centers, Shahram Ebadollahi said.

"This collaboration is in line with our digital transformation," he said. "It is very solutions oriented but

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Sanofi Bets Big On IO With Synthorx Buy

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With the acquisition of US biotech Synthorx Inc. for $2.5bn, Sanofi's new CEO Paul Hudson has confirmed immuno-oncology (IO) as a key focus for the French drugmaker.

Sanofi will pay $68 a share in cash for Synthorx, which represents a 172% premium on its closing price on Friday (6 December). The attraction of Synthorx lies in its lead IO candidate THOR-707, a variant of recombinant interleukin-2 (IL-2), which is in Phase I/II development in multiple tumor types as a single agent and will be investigated in combination with checkpoint inhibitors.

The combo approach is of particular interest to Sanofi which has an approved checkpoint inhibitor of its own. Libtayo (cemiplimab), a PD-1 inhibitor developed with Regeneron Pharmaceuticals Inc., is currently marketed for adults with advanced cutaneous squamous cell carcinoma who cannot have surgery or radiation treatment and is also in trials for a variety of cancers, notably cervical and non-small cell lung. *(Also see "Sanofi's Libtayo Lands In EU With Skin Cancer Nod" - Scrip, 2 Jul, 2019.)*

As well as Libtayo, Sanofi will be looking at "multiple combination opportunities" with THOR-707 and other oncology assets, including its anti-CD38 monoclonal antibody isatuximab, which is currently under review at the US Food and Drug Administration and European Medicines Agency for the treatment of relapsed/refractory multiple myeloma. *(Also see "Sanofi Myeloma Drug Shines But Darzalex Dominates Still " - Scrip, 3 Jun, 2019.)*

Sanofi R&D chief John Reed claimed: "Synthorx's exceptionally novel discovery platform has already produced a molecule that has the potential to become a foundation of the next generation of I-O combination therapies." By selectively expanding the numbers of effector T-cells and natural killer cells in the body, THOR-707 "can be combined with our current oncology medicines and our emerging pipeline of immuno-modulatory agents for treating cancer," he added.

In preclinical studies, because THOR-707 is designed to be a "not-alpha" IL-2, it did not cause the potentially deadly side effect of vascular leak syndrome (VLS) seen with recombinant IL-2 in the past. Synthorx noted that Proleukin (aldesleukin), an IL-2 therapeutic approved by the FDA over 25 years ago and now marketed by the UK's Clinigen Group PLC for renal cell carcinoma and melanoma, has produced "durable clinical responses – and in some cases cures" but its widespread use has been limited by toxicities, which include VLS as well as by its short half-life, requiring IV dosing every eight hours for up to five days. *(Also see "US Rights Deal Will Make Proleukin Clinigen's Biggest Product " - Scrip, 13 Feb, 2019.) (Also see "Novartis, Zurich University Spin-out Anaveon Tackles IL-2 Challenges With Fresh Funds" - Scrip, 1 Mar, 2019.)*

The San Diego-based firm said that THOR-707 was designed to have key advantages over current IL-2 therapies, "such as improved selectivity, increased therapeutic index, ease of use and reduced risk for anti-drug antibodies." It added in combination with checkpoint inhibitors may have greater anti-tumor effects than PD-1 inhibitors alone, without the VLS observed with aldesleukin. *(Also see "Scrip's Rough Guide To IL-2: Mother Of All Cytokines" - Scrip, 26 Mar, 2018.)*

Sanofi's Reed said that Synthorx's pipeline of engineered lymphokines also known as Synthorins, had "great promise not only for oncology but also for addressing many autoimmune and inflammatory diseases." Based on the observation that low doses of IL-2 can dampen immune-cell activation, Synthorx has been evaluating possible opportunities in chronic graft versus host disease, atopic dermatitis and Crohn's disease.

CEO Hudson added that this acquisition "fits perfectly with our strategy to build a portfolio of high-quality assets and to lead with innovation," on which more will be addressed at Sanofi's capital markets day tomorrow (10 December). He claimed the Synthorx purchase was "aligned with our goal to build our oncology franchise with potentially practice-changing medicines and novel combinations.

The deal represents quite a windfall for Synthorx which was founded in 2014 with a platform discovered at The Scripps Research Institute. The La Jolla, CA-headquartered group listed on the NASDAQ almost a year ago to the day, raising $131m from the sale of 11.9m shares at $11 each.

ANALYSTS VIEW

Bryan Garnier analyst Jean-Jacques Le Fur issued a note on 9 December saying that "regarding THOR-707 we estimate that a lot remains to prove especially the interest of having a pegylated IL-2 compared to a traditional one and to show higher efficacy. Therefore, the price paid could appear high."

Analysts at Jefferies described the deal as "an unexpected move," saying "it's clear Sanofi believes that IL-2 will be a backbone of IO therapy." The broker said it does not anticipate any other bids to come in for Synthorx nor does it expect any issues with the US Federal Trade Commission.

There has recently been increased antitrust scrutiny in the US on a number of M&A deals involving overlapping therapeutic areas, notably Celgene Corp. being forced to sell its psoriasis drug Otezla (apremilast) to Amgen Inc. for $13.4bn to win US Federal Trade Commission approval for its merger with Bristol-Myers Squibb Co.. Roche's proposed acquisition of Spark Therapeutics Inc. has been repeatedly delayed and the Swiss major has just announced yet another extension to close the deal to 16 December. *(Also see "FTC Closer To Clearing Roche's Spark Buy: Report" - Scrip, 25 Oct, 2019.)*

More details on the Synthorx acquisition will be given during the capital markets day and Bryan Garnier's Le Fur wrote that Hudson may not provide financial guidance having only been at Sanofi for four months. "We think he will highlight his strategy roadmap from a more general perspective. His challenge … will be to convince investors that they can have confidence in a return to sustainable earnings per share growth," he said, adding that the focus will probably be on R&D and the strategy to replenish the pipeline. *(Also see "The Challenges Facing Paul Hudson At the Helm of Sanofi " - Scrip, 7 Jun, 2019.)*.

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anchored in machine learning and AI to create these Insight centers for monitoring real time with analytics to help make better business decisions and to increase efficiency in our manufacturing and supply chain."

Novartis CEO Vas Narasimhan has regularly emphasized that automation and culture change is needed at Novartis to improve its overall performance. *(Also see "Strategy At Novartis: Culture Change As The 'How' Behind The 'What'" - In Vivo, 19 Nov, 2018.)*

"This new platform will enable Novartis to transform the way it manufactures and delivers medicines, meaning new treatments can be made available to patients faster," Ebadollahi summarized.

The collaboration with Amazon Web Services should enable manufacturing and planning teams at Novartis to better forecast and track production lines, detect potential bottlenecks, and perform predictive maintenance of machines, and have adjustments made automatically to enhance accuracy.

Novartis plans to use Amazon's AWS IoT (Internet of Things) services to visualize data that can then be assessed using computer vision algorithms that monitor for risks to manufacturing production. These include unplanned downtime, out of stock inventory, or delayed orders.

"When this is up and running with this real-time data, Novartis will be able to automatically take corrective action to ensure that medicines are more efficiently produced and distributed to almost 1 billion patients in 155 countries around the world," Ebadollahi said.

"This collaboration begins immediately and hopefully we'll see some good results from it by mid-2020. It promises to be transformational for us," he added.

No financial or investment details were given.

"Our CEO Vas Narasimhan has often said that transforming the company is a key objective, through the importing of, the collaborating around, and the development of technology," Ebadollahi explained.

The collaboration with Amazon is consistent with Novartis's SENSE operations center in Basel which monitors hundreds of clinical trials worldwide. *(Also see "How Novartis Is Making SENSE Of Clinical Data In Digital Age" - Scrip, 6 Feb, 2019.)*

"This collaboration is different but will build on the success of our SENSE operations center."

"The Insight centers that we are going to build for our technical operations will be used both at the local level within at individual manufacturing sites, and also employed globally."

"This alliance will span multiple years. It's not just for one project. One thing I'm really excited about is learning from the likes of AWS and by extension Amazon about new ways of working," Ebadollahi said.

"The physical transformation this will bring is not just about tools and technology – although that's an important ingredient – but also the way of working, acquiring the mindset needed for developing these kinds of solutions and digital expertise, and doing so through a collaboration like this."

"This will contribute to the data science - and the culture of data science - at Novartis," he concluded.

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Neurocrine Adds Epilepsy Assets From Xenon

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Neurocrine Biosciences Inc. is continuing to bring in assets through a new partnership with Xenon Pharmaceuticals Inc. that adds epilepsy candidates to its pipeline and funds an R&D collaboration with the smaller firm, which enables Xenon to focus more on a pair of Phase II epilepsy candidates it wants to take to market on its own.

Neurocrine announced 2 December that it will pay $50m up front – divided between cash and equity – to obtain worldwide rights to Phase II-ready XEN901, a selective Nav1.6 sodium channel inhibitor. The agreement also gives Neurocrine rights to preclinical Nav1.6 and dual Nav1.2/1.6 inhibitors and funds a multi-year collaboration with Xenon to discover and develop additional compounds in those classes.

It's Neurocrine's second deal of the year, following a late January tie-up with Voyager on gene therapy candidates for Parkinson's disease and Friedreich's ataxia with a $165m upfront payment, including $115m in cash and $50m in equity. *(Also see "Voyager Nabs Neurocrine As Partner In CNS Gene Therapy" - Scrip, 29 Jan, 2019.)* San Diego-based Neurocrine markets Ingrezza (valbenazine) for tardive dyskinesia, a product showing steady growth with sales of $515m through the first three quarters of 2019, after banking $410m in 2018.

Both the Voyager and Xenon transactions outlines up to $1.7bn in development, regulatory and commercial milestone fees for Neurocrine's partner.

On a same-day investor call, Xenon CEO Simon Pimstone said the costly effort to develop XEN901 fits better in the hands of the wealthier Neurocrine, while his company adds to its financial runway and can put full focus into Phase II epilepsy candidates XEN496 and XEN1101. The former, a Kv7 potassium channel modulator, could enter Phase III early in 2020, the exec said, while the latter is expected to produce Phase II data by the end of 2020.

A Kv7 potassium channel opener, XEN1101 could be an "only-in-class" therapy for focal seizures, Pimstone asserted, offering differentiation from current anti-seizure medications.

"Recognizing the opportunity for multiple indications, and therefore the need for significant investment in XEN901 and next-generation sodium channel candidates," Pimstone said, "we made the strategic decision to seek a partnership to allow us to more comprehensively develop the sodium channel assets, while also investing more heavily in our retained assets, which we believe offer a very significant promise."

DEAL TERMS BRING XENON MULTIPLE OPPORTUNITIES

The upfront payment from Neurocrine to Xenon includes a $20m equity stake, priced at $14.20 per share, which Xenon president Ian Mortimer called a significant premium to the biotech's average trading price in recent months. Xenon also can earn a near-

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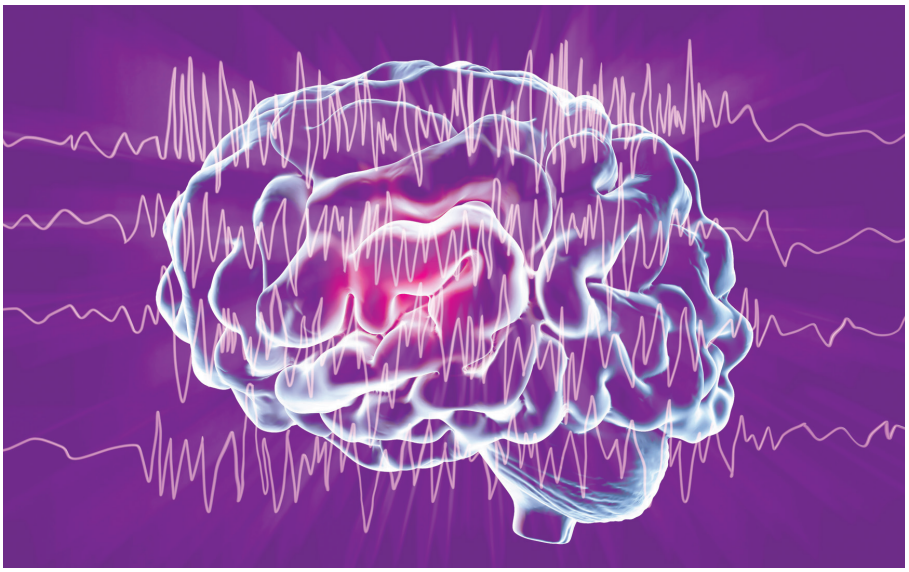

term milestone of $25m upon Neurocrine filing an investigational new drug (IND) application with the US Food and Drug Administration to advance XEN901 into a placebo-controlled Phase II study in SCN8A developmental and epileptic encephalopathy (SCN8A-DEE). Fifty-five percent of that milestone fee would be a further equity investment by Neurocrine at a 15% premium to Xenon's volume-weighted average share price over the prior 30 days.

Mortimer told the investor call he thinks this is the largest deal around a pre-Phase III epilepsy candidate to date. "We have secured excellent terms for a pre-efficacy asset, and we believe we have struck the right balance between near-term cash through the upfront payment, near-term milestone opportunities and collaboration funding with longer-term value creation opportunities through significant development milestones and participation in commercial success," he said, adding that the deal likely extends Xenon's cash runway from 2021 into 2022.

In addition to the up to $1.7bn for milestones and tiered sales royalties tied to XEN901 and the other Nav1.6 and Nav1.2/1.6 inhibitors covered by the deal, Neurocrine funds all development costs for these programs along with a research collaboration of up to three years (specified at a minimum of 10 full-time equivalent personnel). Xenon also holds an option to fund 50% of the US development costs of XEN901 or another candidate in exchange for increased royalties up to 20% of US sales.

Neurocrine thinks XEN901 offers potential in multiple epilepsy indications.

DEVELOPING SPECIALTY FOR NEUROCRINE

Credit Suisse analyst Evan Seigerman applauded the deal from Neurocrine's perspective in a same-day note, saying it strengthens the company's "pipeline optionality" and adds an encouraging opportunity in epilepsy.

SVB Leerink analyst Marc Goodman took a similar view on 2 December, saying investors will be intrigued by the opportunity the collaboration brings to Neurocrine as new mechanisms of action are showing potential in epilepsy. Specifically, he cited the recent approvals of Zogenix Inc.'s Fintepla (low-dose fenfluramine) and GW Pharmaceuticals PLC's Epidiolex (cannabidiol) for rare forms of epilepsy, such as Dravet syndrome. *(Also see "Zogenix' ZX008 Emerges As Strong Contender In Rare Epilepsy" - Scrip, 12 Jul, 2018.)*

Goodman pointed out that Neurocrine plans to target both SCN8A-DEE – an ultra-orphan indication thought to have well under 1,000 patients – and the broader indication of focal epilepsy in adults. XEN901's mechanism of action may offer a better therapeutic index than Nav channel drugs that aren't selective inhibitors, he added.

"We believe targeting the Nav1.6 sodium channel makes sense as there is ample scientific literature and human genetic evidence indicating that mutations of the SCN8A gene impact this sodium channel's behavior and function," Goodman wrote. "Current anti-epileptic drugs such as phenytoin, carbamazepine and lacosamide target Nav channels more broadly, which can serve as directional proof-of-concept in epilepsy, but XEN901 is differentiated as it is designed to specifically target the Nav1.6 channel, which is the most highly expressed sodium channel in the excitatory pathways in the central nervous system."

In addition to VY-AADC, a Phase II candidate obtained in the Voyager partnership, Neurocrine's pipeline also includes Phase II NBI-74788 in congenital adrenal hyperplasia, North American rights to Bial-Portela & CA SA's Phase III Parkinson's candidate opicapone (FDA action date 26 April 2020) and a Phase III label-expansion effort for valbenazine in Huntington's chorea.

Pimstone said his company's expertise in neuroscience and ion channel modulation should be complementary with Neurocrine's clinical development and commercial experience in neurology.

"We believe we have strong rationale for specifically inhibiting the Nav1.6 and Nav1.2/1.6 channels as a therapeutic strategy for diseases of hyperexcitability, including epilepsy," the Xenon CEO said. "However, this therapeutic approach has not been tested clinically and will likely require intense and broad development. That is why we think that Neurocrine's investment into XEN901 and related preclinical assets provides us the greatest probability of success to test our thesis broadly with numerous compounds having different properties and profiles in different indications."

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LET'S GET SOCIAL
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Lilly Taps Loxo Execs To Bring Back That Biotech Feeling

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Eli Lilly & Co.'s turnaround in oncology has been a long time coming. It's been a historic focus for the Indianapolis-based biopharma, and the company has made some sizeable additions in recent years to build out its oncology business. Now the company is leveraging its acquisition of Loxo Oncology Inc. to establish a new cancer R&D unit led by former Loxo execs and incorporating personnel from Lilly Research Laboratories.

Big pharmas have a history of trying to replicate the nimbleness and efficiency of a biotech company within their larger organization. And companies often try to maintain the success of an acquired company by letting it operate somewhat independently of the parent corporation – such as Gilead Sciences Inc.'s decision with Kite Pharma Inc. earlier this year.

Roche offers a close parallel to Lilly's new move, as it has kept Genentech Inc. as a separate entity in many ways since the 2009 buyout, with its own governance, budget partnering teams and portfolio. *(Also see "Genentech's Early Cancer Technology Scout On Partnering, Roche Setup & BD Challenges" - Scrip, 30 Mar, 2017.)* Its Genentech Early Research and Development (gRED) unit is an independent, autonomous R&D unit within Roche, driving much of the pharma's oncology drug development.

With the early successes Loxo has brought to Lilly, the company is hoping that the biotech's old management team can offer an insightful approach to oncology discovery and R&D, including through deal-making. Announcing the new structure, Lilly said the unit will "curate a balanced pipeline of medicines – whether internally or externally discovered" to help gain Lilly a leadership position in oncology.

In addition to adding to the pipeline via business development, the unit, to be called Loxo Oncology at Lilly, will oversee cancer R&D regardless of the therapeutic modality and also oversee clinical development and regulatory affairs. Once a drug candidate approaches commercialization, it will be turned over to the Lilly Oncology Business Unit headed by senior vice president/Lilly Oncology president Anne White, the company announced 5 December.

Leading the new unit will be former Loxo CEO Josh Bilenker, who recently became the pharma's acting oncology chief when former senior VP-oncology R&D Levi Garraway departed after three years to become Roche's chief medical officer and head of global product development. *(Also see "Roche's New Chief Medical Officer Levi Garraway Brings Deep Cancer Genomics Expertise" - Scrip, 19 Aug, 2019.)* It was only July 2017 when Garraway and then Lilly Oncology president Susan Mahony laid out a revised cancer strategy that would center on foundational therapies that "inhibit a key dependency within the tumor." *(Also see "Lilly Hopes To Revitalize Its Cancer Brand With 'Foundational' Agents" - Scrip, 25 Jul, 2017.)*

The January 2019 acquisition of Loxo was a major move in that direction.

Joining Bilenker in the leadership of Loxo Oncology at Lilly will be former Loxo chief operating officer Jake Van Naarden and former chief development officer Nisha Nanda. In addition, David Hyman, currently the head of early drug development at Memorial Sloan Kettering Cancer Center, will join the team in January as its chief medical officer. The unit will report to Lilly chief scientific officer Daniel Skovronsky.

When Lilly acquired Loxo in January, it placed a significant bet on that company's tumor-agnostic, genetic approach to selecting patients and treating cancer. *(Also see "Lift-Off For Lilly In Cancer Genetics With Loxo Buy" - Scrip, 7 Jan, 2019.)* The $8bn price tag factored out to $235 a share, a 68% premium over Loxo's closing stock price the day before the transaction was announced. But the deal has yielded results already, when RET (rearranged during transfection) kinase inhibitor selpercatinib showed high response rates in thyroid cancer in September, after Lilly already announced it would file the drug for US approval in RET fusion-positive non-small cell lung cancer. *(Also see "Lilly's Loxo Bet Pays Off In Thyroid Cancer, A Second Indication For Selpercatinib" - Scrip, 30 Sep, 2019.)*

GETTING PAST SOME SETBACKS

That early success offered a contrast to the Phase III failure of Lilly's immuno-oncology candidate pegilodecakin in metastatic pancreatic cancer in October. *(Also see "Lilly's Pegilodecakin Fails Pancreatic Cancer Test" - Scrip, 17 Oct, 2019.)* Lilly still holds out hope for the compound – the basis for the $1.6bn buyout of Armo BioSciences Inc. in 2018 – as a combination agent with checkpoint inhibitors in NSCLC, however.

Shortly after the Loxo deal was announced, Lilly sustained another major cancer R&D setback when its Lartruvo (olaratumab) failed to show an overall survival benefit in soft-tissue sarcoma in a Phase III confirmatory trial supporting its accelerated approval, based on a Phase II study. *(Also see "Lartruvo Phase III Fail Rocks Lilly Oncology Plans" - Scrip, 21 Jan, 2019.)*

In addition to selpercatinib, Lilly said its near-term focus will be on another Loxo candidate, the selective, non-covalent BTK inhibitor LOXO-305 and a pair of internally discovered candidates – LY3499446, a selective covalent KRAS GC12 inhibitor; and LY3484356, a selective estrogen receptor degrader. Lilly did not specify the development stage or cancer type for either of the latter two molecules.

Lilly is scheduled to present data on LOXO-305, however, at the American Society of Hematology annual meeting 7-10 December in Orlando, including interim Phase I data from a Phase I/II study in B-cell malignancies. Also at ASH, the pharma will present preclinical data activity in Imbruvica (ibrutinib)-resistant chronic lymphocytic leukemia (CLL) and a poster on the drug's activity against various BTK substitution mutations.

The Loxo Oncology team will also be charged with adding to the pipeline through acquisition and in-licensing opportunities, with Skovronsky saying Lilly hopes to incorporate the Loxo discovery and development philosophy "at a much larger scale." Lilly also stated several early-stage clinical oncology candidates will be "wound down and terminated," with disclosure of which candidates slated for the pharma's fourth quarter 2019 earnings call in early 2020.

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Currently, Lilly's pipeline lists more than a dozen clinical candidates for oncology, including label-expansion efforts for Verzenio (abemaciclib) into adjuvant and HER2-positive metastatic breast cancer and Cyramza (ramucirumab) in NSCLC.

In addition to the Verzenio supplemental indications and olaratumab, pegilodecakin and selpercatinib, the Phase II pipeline includes LY3200882, a TGF beta receptor 1 kinase inhibitor being studied for undisclosed cancer indications. The Phase I pipeline lists seven assets, including three immune-oncology candidates targeting IDO1, PD-1/PD-L1 and TIM-3, but details on those candidates are scant. Lilly's recent cancer efforts also include a partnership signed in October 2017 with Germany's CureVac AG to investigate potential next-generation cancer vaccines. *(Also see "Lilly's Billion-Dollar Deal With CureVac For 'Next Generation' Immunotherapies" - Scrip, 19 Oct, 2017.)*

SKOVRONSKY TALKS UP PIPELINE

Speaking at the Evercore ISI HealthCONx conference 4 December, Skovronsky betrayed no hints that a major reshuffling of Lilly's cancer R&D engine was imminent. While also discussing the pharma's R&D efforts in type 2 diabetes and Alzheimer's disease, the exec said Lilly is hopeful that data from the Cypress 1 study of pegilodecakin in first-line lung cancer, expected during the first half of 2020, will yield better results than the previous study in pancreatic cancer. He asserted that there should be little read-through from the drug's results in pancreatic cancer to its potential efficacy in lung cancer.

"When we acquired Armo and acquired pegilodecakin, we commented that this is something that we see as a high-risk/high-reward opportunity," Skovronsky noted. "I think the risk profile is different in different indications for sure. And probably, we saw pancreatic cancer as the highest-risk trial. Armo had started that Phase III when we acquired the company and the asset, and so we weren't in a position to stop the trial."

In NSCLC, the study is investigating the combination of pegilodecakin with Merck & Co. Inc.'s Keytruda (pembrolizumab) versus Keytruda monotherapy.

"The hope, if this drug is active in this population, is that we'll see a pretty wide margin in efficacy. I think it would have to be given the fact that there are alternatives to patients that IO monotherapy can be surpassed with, for example, a KEYNOTE-189 [Keytruda plus chemotherapy] regimen," he said. "So, for me, the question is how much space, first of all, can we differentiate and then how big is the gap? Because I think if we go on to registration-type trials, we'll need to have a significant improvement over monotherapy or have a different comparator there.

"But also, we'll be able to read through from that trial to the activity of the agent in general, which could inform subsequent investigations," Skovronsky continued. "So, for example, IO failures could be an interesting population. Another interesting population is RCC, renal cell carcinoma patients, where there was some activity in the Phase I study from Armo."

The exec also said he's confident that selpercatinib holds a best-in-class profile among RET inhibitors. "Patients haven't been on this drug that long, but the durability data continues to be very impressive," he said. "I think it has set a very high bar for any follow-on competitors."

"We also have all of the attributes we wanted," Skovronsky added. "We have extraordinary intracranial activity, which is very important. We have activity against gatekeeper mutations, which we fully expected and saw. And we have a specificity profile. That means we don't have any off-target safety issues."

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What Lies Beneath China's Steep Price Cuts For New Drugs

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The dust may have settled but the debate is just starting.

As soon as the 2019 version of the China National Reimbursement Drug List (NRDL) was out, there was a rush of celebration among companies whose products were included in the list. Some companies even seemed to have already prepared their press statements, releasing them just after the 28 November official announcement.

Several multinational drug makers including Merck & Co. Inc., Novartis AG, Sanofi and Roche put out releases close on the heels of the announcement released by the National Health Security Administration.

Novartis, in a post on the popular Chinese social portal WeChat, hailed that seven of its products had been included in the list, including Entresto (sacubitril/valsartan), Lucentis (ranibizumab), Afinitor (everolimus). The Swiss drug maker also noted that 20 drugs have been covered since 2017 when the last NRDL was updated.

French firm Sanofi also put a WeChat statement announcing three product inclusions: Aubagio (teriflunomide), Renagel (sevelamer) and Lyxumia (lixisenatide).

Steep Price Cuts In Exchange For Coverage May Not Be Worth Celebrating, One Insider Says

US drug maker Gilead Sciences Inc. is among those that have seen one of the deepest price cuts; two of its direct acting agent hepatitis C drugs, Epclusa (sofosbuvir and velpatasvir)

and Harvoni (ledipasvir and sofosbuvir) were among three HCV treatments that have seen on average 85% price cuts. Gilead executive expect the coverage to expand access to the drugs in China.

"It's unprecedented that four new products can get reimbursement just after around one year of launch," noted Roger Luo, Gilead China GM via a LinkedIn post. "It's a new milestone for Gilead China after we got seven new products approved in the last two years…in 2019, there will be 60,000-plus patients who can benefit from our innovative products."

In an interview with China state broadcaster CCTV, Luo said the prices will "allow common Chinese people benefit from these drugs with slashed prices, and benefit from value brought by the latest innovation and technologies."

The excitement about expansion of access was echoed by others. Sanofi said the inclusion will allow timely access to new treatments, increasing patients access and reducing disease burden.

LOW PARTICIPATION, STEEP CUTS, UNPREDICTABLE OUTCOME

However, one industry insider told *Scrip* that the decision to slash prices this deep in exchange for the coverage is much more complex.

For one, out of 119 newly approved drugs that qualified for the reimbursement coverage, 70 drugs were eventually included, leaving 49 (or over 40% of drugs) not included in the list. Not only products from multinational drug makers, four of 12 Chinese domestically developed novel new drugs were not included as there was no agreement on the pricing.

Secondly, the average prices were slashed by 60.7% across the board, a 65% cut for cancer drugs and antidiabetes therapies and 85% discount for hepatitis C treatments. "Many globally well-known and high-priced drugs are now at prices that are affordable to common people, nearly all important drugs are now offered at global low prices," hailed the government in a statement 28 November.

But the industry insider noted that "participation is low, the price cuts are steep, and the outcome is still hard to tell".

First, competition had made the decision to get the coverage more urgent than two years ago when the price negotiation mechanism was first introduced to be part of the reimbursement process.

The competitiveness is evident among high-priced novel products including immune-oncology drugs. Already, there are five PD-1 drugs approved and launched in China, including Opdivo (nivolumab) from BMS and Keytruda (pembrolizumab) from Merck & Co, and three domestic antibodies, plus one more coming. In order to compete in the crowd, makers are elbowing out each other to get coverage with lowered prices, but still, only one PD-1, Tyvyt (sintilimab) from Innovent Bio received NRDL coverage.

SELECTION PROCESS STIRS UP COMPETITIVENESS

The largest revamp to the national medical coverage list, the 2019 NDRL and price negotiation is a competitive process, especially for widely prescribed drugs such as direct acting agent (DAA) hepatitis C drugs that will treat millions of patients in China.

The process starts from the selection of candidates to be included in the list by an extremely large pool of physicians, 10,000 in total, and only the drugs selected by them are subject to price negotiations and inclusion consideration.

The sheer number of experts not only present uncertainties but the selection process alone makes the process challenging to predict. The competitiveness is more pronounced in the case of hepatitis C drugs. Unlike for other drugs, government negotiators used an intensely competitive bidding process for HCV drugs, citing that large patient population and high treatment costs associated with them.

The process only allowed two makers to compete for one class of the treatment, noted Xianjun Xiong, director of the National Health Security Administration. "The process is not price negotiation but a price bidding," the insider maintained, adding that it's a diversion of the original design of the process.

China has one of the world's largest HCV carriers, with an estimated 10m people infected, and over 50% of them belong to genotype 1b, according to Gilead.

Another US drug maker Merck & Co whose Zepatier (elbasvir and grazoprevir) was included in the final coverage list, said the competitive process shows the importance the government is placing on HCV treatment.

"There were only two DAA agents for hepatitis genotype 1b included in the list, showing that the government places a high importance to such agents to fight HCV," said Merck China GM Joseph Romanelli in a 28 November statement via the company Wechat platform.

Still, it's too early and hard to predict outcomes of the steep price cuts, the insider stressed, but a right pricing strategy will be top priority for any drug maker eyeing coverage in such negotiations.

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Pharma Finds Its Way in AI

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Pharma has been slower than other industries in fully embracing artificial intelligence technology, Peter Henstock, head of AI and machine learning at Pfizer Inc., told *Scrip* at a recent conference on artificial intelligence and biopharma. He cited a certain wariness in the industry.

"You're taking people who have deep expertise in lots of areas and all of a sudden you're saying there's this new thing that can solve all your problems across the board. And they've heard that before," he said.

AI has taken root in drug discovery, but it has a lot more to offer in drug development, from quickly analyzing numerous medical images and research papers to sorting drug candidates and potential patients.

"All the literature, all the intelligence, can go through AI," he said. "It's going help you figure out which patients are going to benefit, which patients should be studied,

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which patients might be the first to drop out of study, which clinics are the right ones, which biomarkers to target, and which compounds to test. AI is going to change everything in drug development from start to finish."

Pharma is watching, and making definitive, if careful, moves into the space. "There's more buy-in this year than last year," Henstock said.

Some pharma executives suggest that AI and pharma have just started getting to know each other. That process was the focus of the sessions on pharma at the AI World conference in Boston, where drug makers shared their experiences introducing AI to their companies, offering advice for others who want to do the same.

They emphasized that investing in AI should be based on determinations of what's possible, what's necessary and what's valuable.

MAKE THE CASE EARLY & OFTEN

"We are going through big field of change," said Angeli Moeller, AI lead at Bayer AG. Calling the technology a "radical transformation" for pharma, she added that successfully bringing AI into a drug company starts with building the case for investment.

"[Any company would] want to invest in something that gives a top-line and bottom-line impact," Moeller said. "But AI is just a tool. it's just a method. It's just the way you're getting there."

Moeller talked about a data project at Bayer. "They began by really building out the data lake that they need to store the electronic medical records, to interconnect them with the clinical data," she said "But our CFO kept saying, 'No, you've got to start with the value case. Build the data architecture after you've shown the value case works, after you've shown me the return on investment. Then I'll give you money to build data architecture.'

"So you've got to start with the value case," she said. "To your CFO, you can say, for example, this is what your Phase III study cost if we followed a traditional approach. If we use these methods, and if we used the tools that we based on these methods, then this is how much money we'll save you."

Pharma is watching, and making definitive, if careful, moves into the space.

It's not enough to just promise such value, Moeller said. Once the work is underway, there needs to be a way to look in on the process. Regularly checking in with updates should start as soon as there is agreement to fund the AI project.

"It's not 'This has my approval and I will never look at it again,'" Moeller said. "It's that he will track whether or not we deliver on it. Our CFO needs to know what impact we're going to have on our pharma bottom line and top line and he tracks it. We're there, at the executive committee and our board of management on a regular basis presenting our results."

BUILD THE RIGHT TEAM

Presentable results come from having a knowledgeable AI team from the start, said Eduardo Cornejo, AI lead at Sanofi. He added that his company learned that lesson the hard way, after various AI projects failed.

"What we have done in almost two years is to collect all the information about AI projects in the company," he said. "We detected around 40 projects that didn't get [past] the pilot project barrier, which means they didn't go into production. The question is why?"

After a closer look at some of the stalled projects, Sanofi realized its initial mistake.

"It started with us relying on the vendors to put together all the machine learning and the AI components," Cornejo said. It turned out that some vendors Sanofi had chosen simply didn't have experience with large-scale or specialized projects.

"You need to have some baseline before you start building on top of that; if you don't have that, pretty much the vendor is learning AI with us."

Cornejo advises testing a vendor's capabilities before signing a contract. "My first question is, if I send you this PDF are you willing to run it through your tool or your engine – first, to see if it works, and then to give me an outcome?"

Cornejo also noted that Sanofi's past vendors often didn't know enough about health care or pharma to recognize what would work, or not work, for Sanofi. "And [pharma] vendors are supposed to have a health care background."

That's a tougher problem, Pfizer's Henstock agreed, suggesting that, ideally, pharma would have its own AI specialists.

"But it's difficult to get talent," he said. "If you are an expert at AI, would you want to work in pharma, which only sometimes does AI, or a place like Google, which is running it? In pharma, you need people with the AI skills, but who also have the science. And that's a harder fit."

For its part, Sanofi turned its struggles into a set of guidelines for AI teams going forward. As early adopters demonstrate both the potential for AI and machine learning to improve drug discovery and development, more companies will learn from their experiences. That should pave the way forward for the more wholesale embrace of these new technologies that Pfizer's Henstock and others are hoping to see.

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We would like to thank everyone who attended the 15th Annual Scrip Awards, held on 4 December at the Hilton on Park Lane, London.

The evening, hosted by broadcaster Fiona Bruce, was a celebration of excellence across all parts of the pharmaceutical, biotech and allied industries and recognized both corporate and individual achievement.

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Procter & Gamble's Business Development Team

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J&J Quickly Advances BCMA-Targeting CAR-T As JNJ-4528 Shows 100% Response

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Development of Janssen Pharmaceutical Cos.' JNJ-4528 is several months behind the most advanced B-cell maturation antigen (BCMA)-targeting chimeric antigen receptor T-cell (CAR-T) therapy, but the Johnson & Johnson subsidiary is running at full speed to generate pivotal trial results and move into earlier lines of multiple myeloma treatment based on strong Phase Ib responses.

Even so, Bristol-Myers Squibb Co. and its partner bluebird bio Inc. are working hard to maintain the likely first-to-market advantage for their BCMA-targeting CAR-T therapy idecabtagene vicleucel (ide-cel; bb2121). They defended that position by reporting top-line results from the Phase II KarMMa pivotal trial on 6 December – less than 24 hours before Janssen revealed results from the Phase Ib portion of its CARTITUDE-1 clinical trial at a press briefing at the American Society of Hematology (ASH) annual meeting in Orlando, FL.

Bristol recently acquired its share of bb2121 in the nearly $76bn acquisition of Celgene Corp.; the big pharma and bluebird intend to submit the CAR-T therapy for approval by the US Food and Drug Administration and other regulators in the first half of 2020. *(Also see "With Celgene Acquisition Closed, Bristol Faces Major Milestones" - Scrip, 21 Nov, 2019.)* Janssen is attempting to quickly catch up, having fully enrolled the Phase II portion of CARTITUDE-1, which is intended to serve as a pivotal trial. The J&J subsidiary has also moved JNJ-4528 into Phase II and III studies testing the CAR-T therapy in patients who failed fewer lines of therapy than the patients enrolled in CARTITUDE-1.

Bristol and bluebird reported a 73.4% objective response rate (ORR) and 31.3% complete response (CR) rate for bb2121 in 128 relapsed and refractory multiple myeloma patients, who all received at least three prior treatment regimens, with a median of 11.3 months of follow-up in the KarMMa study, setting a high bar for competitors.

However, Janssen's JNJ-4528 also is delivering impressive results, with a 100% ORR at six months for 29 patients with fourth-line-plus multiple myeloma treated with a median dose of 730,000 cells per kilogram, up from a 91% ORR in the ASH abstract released in November when just 21 patients had been assessed.

Among the responses observed in CARTITUDE-1, 69% of patients achieved a CR in the Phase Ib portion of the study, including 66% with stringent CRs. Altogether, 86% of JNJ-4528-treated patients achieved a very good partial response (VGPR) or better while the other 14% had a partial response (PR). All of the evaluable patients achieved minimal residual disease (MRD)-negative status at 28 days post-infusion. At six months, 27 of the 29 patients were progression-free.

"We're seeing a very rapid time to response – the mean time to response is about a month," Janssen's Craig Tendler told *Scrip*. Tendler is vice president of late-stage development and global medical affairs for oncology, hematology and supportive care.

DURABILITY IS KEY

The ability to maintain response is a key issue for CAR-T therapies, with durability of response dependent on continued expansion and persistence of the reengineered T-cells. In the case of autologous treatments like bb2121 and JNJ-4528, a patient's own T-cells are removed, genetically reengineered to target a specific cancer antigen, then infused back into the patient.

Bristol and bluebird reported median duration of response across all three bb2121 doses tested in KarMMa was 10.6 months with median progression-free survival of 8.6 months.

It remains to be seen if JNJ-4528 will meet or beat bb2121's duration of response, but Janssen also was set to report technical data for JNJ-4528 at ASH on 9 December that show expansion of CD8 and CD8-positive CAR-T cells with preferential expansion of CD8-positive T-cells, which "suggest that the high anti-myeloma activity of JNJ-4528 seen at a relatively low T-cell dose is potentially related to its preferential and consistent *in vivo* expansion of CD8-positive CAR-T cells," the company said.

Janssen's partner on JNJ-4528, China's Legend Biotech Corp., also reported updated data at ASH from the LEGEND-2 study conducted in China with LCAR-B38M, which uses the same CAR-T construct as the treatment being tested in CARTITUDE-1. The overall response rate in the new LEGEND-2 data was 88% with a CR rate of 46%; 64% of MRD-negative patients who achieved a CR remain progression-free. Median progression-free survival (PFS) was 20 months, but median PFS for MRD-negative patients was 28 months.

The updated LEGEND-2 results show that many patients remain in response a year later compared with the 88% ORR in 57 patients that Legend reported at ASH in December 2018, including a 74% CR rate. *(Also see "Poseida, Legend/Janssen Look To Snag Celgene/Bluebird's BCMA Crown" - Scrip, 4 Dec, 2018.)*

SAFETY RESULTS COMPARABLE FOR BB2121 AND JNJ-4528

In terms of safety, bb2121 and JNJ-4528 look fairly similar to date with low rates of severe cytokine release syndrome (CRS) and neurotoxicity, which can rapidly escalate in CAR-T-treated patients.

Bristol and bluebird reported that 83.6% (107/128) of patients treated with bb2121 experienced CRS and 18% (23/128) had neurotoxicity. However, grade 3 or higher CRS was observed in only seven patients (5.5%), including one patient who died, and only four patients (3.1%) had grade 3 or higher neurotoxicity events, but there were no grade 4 or 5 events.

Janssen reported that the most common adverse events observed with JNJ-4528 in CARTITUDE-1 were CRS (93%), neutropenia (93%, all grade 3), anemia

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(86%, 55% grade 3) and thrombocytopenia (86%, 69% grade 3). Of the CRS events, 86% were grade 1 or 2, with one grade 3 event and one patient who died of complications from grade 5 CRS at day 99. There were three cases of neurotoxicity (10%), but only one of those was a grade 3 neurotoxic event that occurred together with CRS.

"The safety profile is also very consistent with what was reported previously in the LEGEND study from China with the same CAR-T construct … with the majority of patients experiencing mild to moderate cytokine release syndrome, usually coming on at about seven days and resolving over the next few days," Tendler said. "The neurotoxicity, which is a very important concern, was very, very infrequently observed."

"All of that is so far a very good profile that we think bodes well for a BCMA CAR-T that is differentiated and hopefully should even look better when it's brought into earlier-stage disease," he added.

MORE STUDIES COMING

The Phase II portion of CARTITUDE-1 is fully enrolled and Janssen has initiated two new studies in less advanced patients. The Phase II CARTITUDE-2 trials is enrolling multiple cohorts of multiple myeloma patients, including individuals who are relapsed or refractory after one to three prior lines of therapy, including autologous stem cell transplant; patients who progressed quickly after front-line therapy; and patients who received a prior BCMA-directed therapy.

The Phase III CARTITUDE-4, a randomized trial of JNJ-4528, has not yet begun to enroll patients. This study will evaluate the CAR-T therapy in multiple myeloma patients who are relapsed or refractory after treatment with Bristol/Celgene's Revlimid (lenalidomide) against two other regimens that frequently are used in this population.

The Phase III study's three arms will test JNJ-4528 versus Bristol/Celgene's immunomodulatory agent Pomalyst (pomalidomide) and Takeda Pharmaceutical Co. Ltd.'s proteasome inhibitor Velcade (bortezomib) plus dexamethasone (PVd) and versus the combination of J&J's CD38 inhibitor Darzalex (daratumumab) plus Pomalyst and dexamethasone (DPd). Patients in the JNJ-4528 cohort will receive one or two courses of PVd or DPd plus a short course of immune system-conditioning chemotherapy before infusion with the CAR-T cells.

"We're very much modeling this after what we did for Darzalex, in that when you see very compelling single-agent activity in very, very refractory patient populations we are all-in in terms of broadening the program and focusing on certain patient segments that are at high risk and trying to intervene earlier, where the patient's immune system may actually be at a higher functioning level and therefore you may be able to see better results with the BCMA CAR-T," Tendler said.

"The CAR-T function and their ability to kill tumor cells is very much dependent upon the potency and the strength of the CAR-T, so perhaps if we start with patients with more functional immune systems and more robust T-cells … they may actually be stronger, more effective and in fact hopefully deliver better anti-myeloma activity," he continued.

COMPETITORS COMING IN BCMA CLASS OUTSIDE CAR-TS

While Janssen is moving quickly to catch up with Bristol and bluebird, CAR-T therapies are one of multiple modalities being used to target BCMA in multiple myeloma. GlaxoSmithKline PLC may be first to market with a BCMA-targeting product – the antibody-drug conjugate (ADC) belantamab mafodotin (GSK2857916) – which the company plans to submit for regulatory approvals before the end of this year. *(Also see "DREAMM-2 Put GSK's BCMA Drug In Pole Position In Multiple Myeloma " - Scrip, 23 Aug, 2019.)*

Bispecific therapies also are emerging as competitive options in the BCMA class, including a CAR-T candidate developed by China's Cellyan Therapeutics Co. Ltd. and known as BM38 cells, targeting BCMA and CD38. In Phase I results slated for a 9 December presentation at ASH in 22 fourth-line or greater multiple myeloma patients, including nine with extramedullary tumors, 18 patients (90.9%) treated with BM38 cells had MRD-negative disease after a median of 36 weeks of follow-up. Twelve patients had a stringent CR (54.5%) and seven had a good or very good PR (31.8%). Eight of the nine patients with extramedullary tumors had undetectable tumors. The 17 patients in remission at seven months had a 28.8-week median duration of response. Cellyan is planning a larger Phase II trial for its BM38 cells in the US and China.

Multiple bispecific antibodies targeting BCMA and CD3 are in development as well, including REGN5458 from Regeneron Pharmaceuticals Inc., which presented safety and early clinical activity at ASH in a poster on 8 December. Three patients were treated as of the 12 July abstract cutoff date, including one patient who achieved a VGPR, one with progressive disease and one with stable disease.

Off-the-shelf products, like ADCs and bispecific antibodies, are less complicated, more convenient and likely less expensive than autologous cell therapies, but whether or not they are more effective and/or safer than CAR-T therapies is still an unanswered question.

Nevertheless, Janssen is exploring other BCMA-targeting modalities besides the CAR-T construct used for JNJ-4528 and other multiple myeloma drug targets. The company has two bispecific antibodies – one targeting BCMA and CD3 and another targeting GPRC5D and CD3 – in Phase I. Those antibodies simultaneously target an antigen on cancer cells and a protein on T-cells to recruit the patient's own T-cells to the myeloma cells.

"They are not CAR-Ts; they are meant to have the same ultimate purpose at the end in terms of activating T-cells to destroy myeloma cells, but they are off-the-shelf," Tendler said.

"It's very much in line with our overall mission and strategy in myeloma to utilize all of the agents in our armamentarium and our pipeline and to develop those combination regimens that can really move the science forward and eliminate disease, ultimately to cure some subsets of patients," he continued. "We now actually have some of the best opportunities in our pipeline to move that science forward and really try to eliminate the disease."

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UniQure Aiming To Be First With Hemophilia B Gene Therapy: **https://bit.ly/2LDxjrd**

Biogen's Big Day Arrives, But Aducanumab Results Don't Answer Key Question

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Biogen's closely watched Phase III results for its amyloid-targeting therapy aducanumab in the treatment of patients with early Alzheimer's disease, presented on 5 December at the Clinical Trials in Alzheimer's Disease (CTAD) meeting in San Diego, did not answer a big outstanding question: Can the drug win US Food and Drug Administration approval?

The company presented a complex dataset, including results only for patients treated with the highest dose of aducanumab based on a fourth and final clinical trial protocol change that allowed for patients with the ApoE4 gene to be titrated up to the highest dose. This cut of the data showed statistically significant results for the primary endpoint of change from baseline at 18 months in cognitive decline as assessed by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) in both the EMERGE and ENGAGE studies, whereas in the intent-to-treat analysis with twice as many patients only the EMERGE results for the highest aducanumab dose were statistically significant.

The conflicting datasets could pose challenges at the FDA, since Biogen and its partner Eisai Co. Ltd. will seek approval to treat a disease with several million patients. The Alzheimer's Association estimates that 5.8 million people in the US have Alzheimer's disease and the number will grow to 14 million by 2050.

Biogen has said that the FDA gave the green light for a biologic license application (BLA) filing based on the EMERGE and ENGAGE results, and the company said it will complete the BLA submission early next year, but that doesn't mean approval in the US or elsewhere is guaranteed. Samantha Budd Haeberlein, Biogen's vice president of late-stage clinical development, confirmed during a same-day investor call that the company is preparing global submissions for aducanumab.

Biogen and Eisai are facing skepticism about their filing plans because the companies cut the Phase III EMERGE and ENGAGE trials short in March after an interim futility analysis found the studies were not likely to be successful. *(Also see "Why Biogen/Eisai's Aducanumab Failure Is Not The End Of Amyloid Hypothesis" - Scrip, 21 Mar, 2019.)* The companies then reversed course in October when they said further analysis of the data supports a BLA, which the FDA agreed would be appropriate to submit.

Unanswered: Is FDA approval of aducanumab possible?

With few detailed data points, analysts have spent the last two months debating whether Biogen and Eisai have the right data to not only win FDA approval, but to convince doctors to prescribe the drug and payers to reimburse its potentially high cost. There's no doubt, however, that millions of patients and their caregivers are clamoring for a disease-modifying drug. Aducanumab would be the first-ever Alzheimer's therapy to treat the underlying cause of the disease.

DATA CONTROVERSY ONGOING

Biogen claimed in October that patients treated with the higher of two aducanumab doses in the EMERGE study had a 23% reduction in cognitive decline versus placebo as assessed by CDR-SB, which was statistically significant (p=0.01), while high-dose aducanumab showed an improvement versus placebo in ENGAGE, but the difference was not significant.

The company said at the time that the difference between the results of the two Phase III studies was explained by clinical trial protocol changes that allowed for patients with the ApoE4 gene, which is associated with early diagnosis and rapid progression of Alzheimer's disease, to be retreated after experiencing the potentially serious side effect of amyloid-related imaging abnormalities (ARIA) and to be titrated up to the higher aducanumab dose.

Since ENGAGE began enrolling patients before EMERGE, more patients in EMERGE were exposed to the higher dose – 10mg/kg administered intravenously once monthly – for longer periods of time. Haeberlein indicated in her CTAD presentation of the Phase III data that the median cumulative dose exposure in EMERGE (n=1,643) and ENGAGE (n=1,663) was 116mg/kg before the fourth protocol amendment was implemented and 153mg/kg after.

With that in mind, Haeberlein presented the EMERGE and ENGAGE results separately, but then directed attention to the post-protocol version 4 results for patients treated with 14 monthly infusions of aducanumab at 10mg/kg.

In EMERGE, CDR-SB scores declined by 0.53 points in the high-dose group, which was a 30% difference from the change in the placebo group at 18 months (n=288) in the post-protocol version 4 subgroup. In ENGAGE, CDR-SB scores declined 0.48 points in the high-dose group (n=261), which was a 27% difference from the placebo group. Both were statistically significant.

In the larger intent-to-treat dataset, however, only the EMERGE result was statistically significant at the highest aducanumab dose (n=547), with a 0.40-point decline in CDR-SB scores, representing a 23% reduction versus placebo. In EN-

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GAGE, CDR-SB scores increased by 0.03 points for patients treated with the highest dose of aducanumab (n=555), which was only a 2% difference versus placebo.

SKEPTICISM CONTINUES AS NEW QUESTIONS EMERGE

Many were skeptical of Biogen's explanation for the differences in the EMERGE and ENGAGE results in October when Biogen and Eisai announced their plan to seek approval early next year based on two Phase III studies that were stopped for futility just seven months earlier – skepticism that does not seem to have changed with the new details and subgroup analysis presented at CTAD.

"As many had anticipated, the magnitude of effect on cognitive endpoints was small," Datamonitor Healthcare analyst Pamela Spicer wrote on 5 December. "Looking at just the final data, which will serve as the basis for the FDA filing, ENGAGE failed to demonstrate a statistical benefit on ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale), CDR-SB (Clinical Dementia Rating Scale Sum of Boxes), and MMSE (Mini-Mental State Exam), with the latter endpoints showing numerical worsening."

"In contrast, EMERGE showed miniscule, but significant, improvement on all of these endpoints, achieving less than half of what has been reported to be minimally clinically important differences on these outcomes," Spicer continued. "Looking at the graphs depicting longitudinal changes from baseline seems to show a lack of dose response on CDR-SB and no separation from low dose on ADAS-Cog at weeks 26 and 50 in the EMERGE study. Further, the 78-week results only represent around 50% of the patients in each arm, whereas the 50-week results depict closer to 80% per arm (about 290 versus 430 patients per arm)."

Biomedtracker lowered the likelihood of approval for aducanumab by 6% to 38%, which is 14% below average for Phase III Alzheimer's drugs.

Commenting on a recent *Lancet* publication critical of the strategy to seek approval for aducanumab, Jefferies analyst Michael Yee said in a 4 December note: "At end of the day the fundamental call is the totality of data we see likely do not stack up to FDA rigor typical of approval … so this would be an unprecedented call for FDA to approve based on the data and it would be political pressure that forces the hand."

Yee said in a 5 December note that the question of whether the agency is likely to approve aducanumab based on the current dataset remains unanswered, along with several other questions, such as how many ApoE4 patients were in the protocol 4 subgroup, why response curves for aducanumab improved steeply from week 50 to week 78, what geographical differences there were in the results, whether the results may be impacted by unblinding the studies to investigators and patients, and if stopping and then restarting treatment affected the data readouts.

In response to a question about patients experiencing ARIA and whether this impacted data assessments for those patients, Haeberlein noted during Biogen's investor call that patients with ARIA are aware of what's going on because they may need more imaging or a dose interruption, but the raters who assessed the EMERGE and ENGAGE patients were blinded to whether or not patients had been diagnosed with ARIA.

In terms of whether ARIA will be a problem for prescribers in the real world, if aducanumab is approved, Haeberlein said, "we in our studies and other sponsors have learned a lot about ARIA in the last five years. The vast majority of ARIA does not seem to be problematic." In most cases, patients safely resumed treatment with their prior aducanumab dose, she noted.

"We would never want to dismiss safety, however we would not have implemented these protocol amendments if we had not gotten more comfortable with ARIA, its risks and how to manage it," Biogen executive vice president of R&D and chief medical officer Alfred Sandrock told the company's investor call. Biogen intends to run a re-dosing study, which will give EMERGE and ENGAGE trial participants a chance to get back on aducanumab treatment – or start therapy for the first time if they received a placebo previously.

DOCTORS – PARTICULARLY ADUCANUMAB INVESTIGATORS – CHEER RESULTS

Doctors asked to comment on the aducanumab data were enthusiastic about the results, including physicians who had patients on the drug during the clinical trials, indicating that they expect those patients to enthusiastically resume treatment.

Stephen Salloway, a neurology professor at Brown University, said that "every patient and family is very enthusiastic about returning and being part of that … we've had many studies that have terminated early recently and we haven't had that response with any other treatment."

Similarly, Sharon Cohen, medical director at the Toronto Memory Program in Canada, said "this is exactly the case in Toronto at our site as well," despite the inconvenience of going to the clinic for a monthly infusion.

Salloway, Cohen and Paul Aisen, director of the Alzheimer's Therapeutic Research Institute at the University of Southern California, hailed the EMERGE results in particular as representing a major advance for Alzheimer's treatment.

"The data is complex. I think that the futility decision was highly unfortunate and puts us in the situation of interpreting complex data, but clearly the EMERGE final analysis is positive," Aisen said. "When we consider the difference in the timing of enrollment into ENGAGE relative to the protocol version change and the resulting reduced exposure to the effective high dose of aducanumab, I think the data from ENGAGE and EMERGE can be considered consistent."

"Most patients and providers are likely to endorse this [protocol 4] subset analysis, despite its questionable statistical basis, and for that reason, we expect 'aducanumab excitement' to get even higher," SVB Leerink analyst Geoffrey Porges said in a post-presentation note. "We continue to believe that aducanumab is likely to be approved."

However, most analysts indicated that the data presented at CTAD provided more details, but raised more questions, including Wedbush Securities analyst Laura Chico, who said in a 5 December report that "overall, we continue to hold a cautious view."

Chico noted that "while there is likely to be continued and extensive cuts of the data that emerge, we think the bigger question is the clinical meaningfulness of these results. Panelists, which included investigators from the ENGAGE/EMERGE studies, indicated they see the results as

clinically meaningful; however, there is still the issue of the failed study."

Likewise, Credit Suisse's Evan Seigerman said in a same-day note that "we await further discussion and commentary from KOLs (not just those who believe in the a-beta hypothesis) to better understand if aducanumab can in fact win approval from FDA. While the comparison between the ITT and Post-PV4 data is interesting, we need more context to better understand what could be driving the effect seen on CDR-SB."

Alzheimer's Drug Discovery Foundation founding executive director and chief scientific officer Howard Fillit had a more measured response to Biogen's CTAD presentation, noting that while aducanumab appears to have an effect on Alzheimer's disease at higher doses in a percentage of the EMERGE and ENGAGE populations, more data will be needed to show the drug has a meaningful clinical effect for patients.

Fillit called the studies' results "an incremental step" in advancing the science and potentially getting a disease-modifying drug to patients, but suggested that aducanumab's efficacy may be enhanced by combining it with other types of therapies in development. He said more research in drug development outside of amyloid and on biomarkers of Alzheimer's drug efficacy are needed to advance the field.

ANOTHER TRIAL TO CLEAR UP DATA CONTROVERSY?

Sandrock and Haeberlein declined to provide additional details about the EMERGE and ENGAGE studies during Biogen's investor call beyond the data presented at CTAD. "There's a time and a place for everything. We will soon be under review, so we're sensitive to what we present now," Sandrock said.

Pressed about why the company believes it has data necessary to support approval, he noted that, "we don't file willy-nilly. We only go to filing when we believe there's a benefit/risk argument based on the science and based on the data."

While a new trial could clear up the discrepancy between EMERGE and ENGAGE, Biogen and Eisai may be compelled to push aducanumab toward FDA approval now given competitive dynamics, since Phase III data for Roche's amyloid-targeting biologic gantenerumab – delivered by subcutaneous injection versus aducanumab's intravenous administration – are expected in 2022. An additional study for aducanumab likely would deliver data after the gantenerumab results.

Biogen's Phase I/Ib PRIME study for aducanumab, which immediately preceded the Phase III program, gave the company its initial confidence in the drug because of the reduction in amyloid plaques seen in the brains of Alzheimer's patients and improved cognition, as presented at CTAD in 2016.

However, the company has since had reason to question the amyloid hypothesis – the notion that clearing amyloid-beta from the brain slows Alzheimer's disease progression and potentially improves cognition. There have been years of Phase III failures for other amyloid-targeting therapies; most recently Biogen and Eisai discontinued development of their beta amyloid cleaving enzyme (BACE) inhibitor elenbecestat – the last BACE inhibitor in clinical development – in September.

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GemVax's Novel Peptide For Alzheimer's Set To Advance After Positive Phase II: **https://bit.ly/354QiCT**

Early Assets Excite At Novartis R&D Day

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Novartis AG has presented a detailed look into both early and late-stage assets which it believes could produce 25 potential blockbusters.

At an investor R&D event in London on 5 December, the Swiss major highlighted 60 projects in Phase II, of which at least ten are expected to advance into Phase III each year in 2020 and 2021. Over 90% are projected to be first-in-class or first-in-indication.

Speaking to a small group of journalists hours before the investor event, Jay Bradner, president of the Novartis Institutes for BioMedical Research (NIBR), said "the stars are aligned... because our ability to invest in R&D is directly correlated to the financial performance of the company. These have really been the salad days so in the labs right now, there's quite a lot of optimism and enthusiasm and the productivity is really remarkable."

> "The stars are aligned ... because our ability to invest in R&D is directly correlated to the financial performance of the company." – Jay Bradner

Head of the part of Novartis that discovers drugs and typically takes them up to Phase IIa, Bradner highlighted the firm's portfolio of early-stage molecular "glues" led by TNO155, a first-in-class SHP2 inhibitor. He said this "could be a really big deal" to treat solid tumors and based on preclinical data, has proved to be "powerfully synergistic" with KRAS inhibitors that are being developed for G12C-mutated, non-small cell lung carcinoma.

Novartis announced an agreement in July with Mirati its KRAS G12C inhibitor to test MRTX849 in combination with TNO155. It also made a recent investment in KRAS inhibition for its own portfolio, partnering with Cancer Research UK.

Bradner talked about intermolecular glues, which stick two proteins together. A good example of those are protein degraders, molecules "that take a target protein that's maybe even undruggable and they glue it to the disposal system of the cell to take out the trash and destroy that

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protein." This is the scientific program he runs when not on NIBR leadership duty, and one protein degrader has just entered the clinic, "with a very strong pipeline behind it."

He said, "We've put a huge emphasis on first in class. It may seem obvious but most of biopharmaceutical research is fast-follower research. This illusion of best in class, which I regard as a surrogate for not first in class, is pervasive in our ecosystem and you may know the term 'the best source of new drugs is old drugs.' We reject that hypothesis."

HIGHEST HANGING FRUIT

Saying that Novartis's strategy is "to reach for the highest hanging fruit," Bradner said that "the core of our research engine is now fully rebuilt." This required a change on cultural expectations and management teams "and most importantly, prioritization of our portfolio – research and development were regrettably at quite a distance before."

The portfolio has been overhauled "to engender rapid transit from the labs into the clinics and into the marketplace, through clarified and uniform strategies like you would expect from a vertically-integrated organization," he said. "We've also markedly reduced the scope in order to increase resourcing," with 430 drug discovery projects bring trimmed to about 325.

The R&D day also saw Novartis highlight projects that should be advancing into pivotal trials in the coming years. First up was iscalimab, a monoclonal antibody (mAb) against the CD40 receptor which the firm believes has the potential to become the standard of care in transplant. It has also demonstrated positive proof-of-concept in Sjögren's syndrome, and trials are being initiated in six separate indications. *(Also see "Can Novartis Reclaim Pioneering Role In Transplantation? " - In Vivo, 2 Oct, 2019.)*

Also causing excitement was LNP023, an oral factor B inhibitor which targets the alternative complement pathway. Novartis claimed that early Phase II data support advancing the drug as a first-line treatment for the rare blood disorder paroxysmal nocturnal hemoglobinuria (PNH).

Full Phase IIa/IIb readouts are expected next year and 20021 for LNP023. It is in development for three rare renal diseases – IgA nephropathy, membranous nephropathy and C3 glomerulopathy.

In immuno-oncology, the Basel-based group touted MBG453 as a first-in-class anti-TIM-3 mAb which it thinks has the potential to become a foundational therapy across myeloid diseases. It is currently in a pivotal Phase II program in myelodysplastic syndrome, with Phase I data to be presented at the imminent American Society of Hematology (ASH) meeting in Orlando.

Another asset that will be moving into late-stage trials next year is TQJ230, an antisense oligonucleotide to reduce lipoprotein(a) a currently untreatable risk factor for cardiovascular disease. A CV outcomes trial of over 7,500 patients evaluating the RNA-targeting lipid-lowering candidates recently licensed from Ionis Pharmaceuticals Inc. affiliate Akcea Therapeutics Inc. is planned to start in 2020.

The drug is key to Novartis's CV efforts which have just received a boost with its proposed $9.7bn acquisition of The Medicines Company and the latter's closely-watched siRNA drug inclisiran. *(Also see "It Has Been A Long Farewell To The Medicines Company" - Scrip, 26 Nov, 2019.)*

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Novartis Targets Ten Indications For Cosentyx: **https://bit.ly/2PG1yzh**

Sage Still Sees Approval Path After Depression Drug Fails In Phase III Trial

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Sage Therapeutics Inc. executives are positioning the failed MOUNTAIN trial of its antidepressant SAGE-217 as more of a molehill and suggesting that the data could still be supportive of a new drug submission to the US Food & Drug Administration.

The firm announced SAGE-217 had missed the primary endpoint in the Phase III trial in acute treatment of major depressive disorder. However, the company's review of the data indicates that there was a problem with compliance, as many patients had no detectable level of drug in their blood, and that there was a high number of patients with less severe de-

The Phase III MOUNTAIN trial missed the primary endpoint

pression. Reanalysis of patients with more severe MDD showed a significant effect for SAGE-217.

Sage chief medical officer Stephen Kanes told a 5 December investor call that the company is currently thinking "about how we can use the data at hand, including the results from this study which we referred to as supportive, to put together a filing," noting that Sage is in "ongoing talks with the FDA."

Sage is banking on the appeal of a new treatment paradigm unlike that of other oral antidepressants, which require daily maintenance doses to control the condition. SAGE-217, a next-generation positive allosteric modulator optimized for selectivity to synaptic and extrasynaptic GABA-A receptors, is taken for only two weeks and then stopped. The drug is seen as an oral successor to Sage's postpartum depression drug Zulresso. *(Also see "Sage's Zulresso Launch Is Off, But Not Running " - Scrip, 6 Aug, 2019.)*

REANALYSIS SHOWS SUCCESS

In the MOUNTAIN trial, 581 randomized patients received nightly doses of 20mg, 30mg, or a placebo for two weeks. The 30mg dose was associated with a mean reduction of 12.6 in the Hamilton Rating Scale for Depression (HAM-D) total score after two weeks, compared to 11.2 for placebo (p=0.115). The 20mg dose of SAGE-217 did not show a difference from placebo.

CEO Jeff Jonas told the call that there were two factors potentially affecting trial results. For one thing Sage's post hoc analysis of the patient blood-level measurements found that 9% of the 30mg group had no measurable drug concentration.

"This is a long half-life drug and the assay is sensitive down literally to the nanogram level. So they had undetectable drug," he said. Patients were assessed at day 8 and day 15, and "given the pharmacokinetics of the drug and the sensitivity of the assay and the time point that we sampled, they weren't taking drug. There's just no other explanation for it. So that's it. So they just didn't take drug."

After excluding these patients from the analysis, the company found there was a statistically significant improvement at all timepoints through and including Day 15 (-13.0 for 30mg vs. -11.2 for placebo at Day 15, p<0.048).

Jonas also said that the MOUNTAIN study enrolled more patients with a milder severity of symptoms (less than 24 on the HAM-D scale) than had been enrolled in previous studies of SAGE-217. "Patients with milder symptoms are more heterogeneous, have a more variable response, and of course, statistically, there is numerically less room for improvement," he said.

When including only patients with a HAM-D of at least 24 (n=124 for SAGE-217 30mg), a post-hoc analysis demonstrated statistical significance at all timepoints through and including Day 15 (-13.7 for 30mg vs. -11.4 for placebo at Day 15, p<0.032). Analyses utilizing a HAM-D cutoff of 25 or 26 were also statistically significant, the company reported.

The company noted that there was rapid onset, with effect showing at Day 3, and that improvements in depressive symptoms were sustained in all treatment groups through Day 42 of the double-blind portion of the study. Long-term follow-up data will be collected at six months.

Secondary endpoints included the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HAM-A) total score, among others, but Sage is not releasing secondary endpoint results at this time.

FILING PLANNED, BUT UNCLEAR

Sage management attempted to assure investors and analysts that the totality of the data will support FDA approval of SAGE-217, declining to provide clarity about its regulatory plans or address whether it would conduct another study. The drug has already succeeded in one Phase III trial in MDD, and two more – SHORELINE (retreatment) and RAINFOREST (comorbid MDD and insomnia) – will report out in 2020. In addition, the drug has succeeded in a Phase III trial in postpartum depression. *(Also see "Sage Impresses With Second Postpartum Depression Therapy" - Scrip, 8 Jan, 2019.)* Execs also noted that SAGE-217 has breakthrough designation, so the firm is in close consultation with the FDA.

"We view this study as … strongly supportive of a generalized MDD filing," Jonas told the call. "Even if you just look at the data we presented, if you look at forest plots, it's all in the right direction in terms of drug activity. So I think at this point, our plans are going to remain the same. We have other studies that will really completely inform how this drug ought to be used. We're encouraged by the maintenance data we've seen here. So I think our intent right now is, based on the data from this study, is that the pathway to MDD and PPD combined remains open for us."

Jonas did say that MOUNTAIN's results suggest that Sage rethink study methodology.

"Ultimately, what we'll do is we'll look at the procedures, not the data but the procedures that are going on in the ongoing studies and see if there's anything we need to amend," he said.

ANALYSTS HOPE FOR ANOTHER TRIAL

Jeffries analyst Andrew Tsai commented that the company's next steps were "murky" and suggested that Sage's options might become clearer as it releases SAGE-217 trial results from the other major depression studies. "Our base case assumption is for Sage to 'wait' until 2-3 of the MDD expansion studies readout, since company believes at least one of those could serve as a 'backup' pivotal," he said in a 5 December note.

Meanwhile, analyst Tim Lugo of William Blair found some encouragement in the post-hoc data. "We do not view it as a complete failure for the program given the continued rapid effect of SAGE-217."

Lugo also noted Sage's "strong pipeline" of neurological and psychiatric drugs, said, "We still see potential for SAGE-217 in several depressive disorders. There is a precedent for approval with [Johnson & Johnson's] Spravato, which was approved based on a positive Phase II study and a positive Phase III relapse prevention study after failing a prior Phase III study."

The company's stock fell 50.7% on the news, closing at $60.18.

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Acadia's Nuplazid Shows Nearly Three-Fold Reduction In Psychosis Relapse

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The market for Acadia Pharmaceuticals Inc.'s Nuplazid (pimavanserin) could grow to 10 times its current Parkinson's disease psychosis population if it is approved to treat dementia-related psychosis based on the results of a Phase III study presented on 4 December at the Clinical Trials on Alzheimer's Disease (CTAD) conference in San Diego.

Acadia stopped the Phase III HARMONY trial early in September based on positive interim efficacy, and in data presented at CTAD the company showed that dementia patients treated with pimavanserin were 2.8 times less likely to have a psychotic relapse than those who received a placebo during the randomized portion of the study. San Diego-based Acadia will submit a supplemental new drug application (sNDA) for pimavanserin in the treatment of dementia-related psychosis (DRP) to the US Food and Drug Administration in 2020 based on these results.

CEO Steve Davis told *Scrip* that the drug's efficacy and safety make it an attractive alternative to atypical antipsychotics currently used off-label to treat DRP – an indication with no approved therapies. In fact, no new drugs have been approved to treat dementia in 15 years, he noted.

"These are patients that carry high disease burden to start with and when you layer psychosis on top of the cognitive deficits that they have, the burden of dementia is really a lot to carry," Davis said. "So, if we can help them by treating the psychosis symptoms, I think you have a very high impact on people."

University of California, Los Angeles psychiatry, behavioral sciences and aging professor Gary Small, who also is director of the UCLA Longevity Center and the geriatric psychiatry division at the Semel Institute for Neuroscience & Human Behavior, noted during Acadia's 4 December investor event that not only are there no approved drugs for DRP, but the treatments that are used do not work well. Small said based on the HARMONY data, pimavanserin is a good option regardless of the cause of the dementia – Alzheimer's disease or otherwise.

"It's encouraging to me that as a clinician that if I prescribe this drug there's a pretty good chance the patient is going to respond," he commented on the investor call.

PIMAVANSERIN CUT DRP RISK SIGNIFICANTLY

All 392 DRP patients enrolled in the HARMONY study were treated with 34mg of pimavanserin once-daily in a 12-week open-label period; while dosing could be reduced as needed to 20mg during the first four weeks, 90% of the trial participants remained on the 34mg dose.

Individuals who responded to the drug based on assessments at weeks eight and 12 moved into the study's randomized portion, where they were treated with pimavanserin (n=105) or placebo (n=112) for 26 weeks (six months) or until relapse. Relapse was defined as hospitalization due to DRP, significant deterioration of dementia-related symptoms on clinical scales, withdrawal from the study or use of another antipsychotic drug to manage hallucinations and delusions.

Acadia reported that 61.8% of the patients enrolled in the open-label portion of HARMONY responded to treatment. Psychosis symptoms as measured by the Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions (SAPS-H+D) improved by 75.2% from baseline to week 12 (73.1%-83.3% depending on the dementia subtype).

Pimavanserin met the primary endpoint of time to relapse in the randomized portion of HARMONY by reducing the risk of psychotic exacerbation by 63% versus placebo (HR=0.353, p=0.0023), which means that pimavanserin prevented relapse at a rate 2.8 times that seen in the placebo group. On a secondary endpoint related to the risk of treatment discontinuation for any reason, pimavanserin-treated patients saw a 55% risk reduction versus those who received a placebo (HR=0.452, p=0.0024) – a 2.2-fold difference.

Adverse event rates in the randomized portion of HARMONY were 41% for pimavanserin and 36.6% for placebo, while serious adverse event rates were 4.8% for pimavanserin and 3.6% for placebo. The most common side effects were headache (9.5% for pimavanserin versus 4.5% for placebo) and urinary tract infections (6.7% versus 3.6%). Despite higher rates of adverse events for Acadia's drug, treatment discontinuation rates were lower for pimavanserin at 2.9% versus 3.6% for placebo.

There was one death during the open-label portion of the trial and another death in the pimavanserin arm of the randomized portion, but HARMONY investigators determined than neither death was related to the study drug.

Safety concerns had been raised in 2018 based on adverse event reports since Nuplazid's first approval in 2016, but the FDA determined that the severe side effects and deaths reported were consistent with the drug's label and its elderly Parkinson's disease population.

Davis said there are three important takeaways from the HARMONY results.

"The first is in the open-label portion of the study we saw that pimavanserin showed a meaningful reduction and stabilization of the symptoms of psychosis over five clinically dosed subtypes [of DRP]; being able to stabilize these patients during that 12-week open-label period was a very meaningful finding [and] it's consistent with what we've seen in previous studies," he noted.

"Second, in the double-blind period patients on placebo were almost three times more likely to experience a psychotic relapse compared to pimavanserin," Davis continued. "Third, in this study, as we expected based on previous studies, pimavanserin was very well tolerated."

In terms of safety and tolerability, he said that what was most important in this elderly population with multiple comorbidities is that there was no negative impact on cognition.

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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, 29 NOVEMBER–5 DECEMBER 2019

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	AVEO Pharmaceuticals, Inc.	tivozanib	Renal Cell Cancer	TIVO-3; The Lancet Oncology, 3 Dec, 2019	0	27
Phase III Updated Results	AB Science S.A.	masitinib	Asthma	AB07015; Encouraging Results	0	68
Phase III Updated Results	Acadia Pharmaceuticals, Inc.	Nuplazid (pimavanserin)	Dementia In Alzheimer's Disease	HARMONY; Met Primary Endpoint	0	60
Phase III Updated Results	Biogen, Inc.	aducanumab	Alzheimer's Disease	EMERGE, ENGAGE; Mixed Results	-6	38
Phase IIb/III Top-Line Results	Evofem Biosciences, Inc.	Amphora (pH regulating salts)	Chlamydia, Gonorrhea In Women	AMPREVENCE; Positive Results	4	65
Phase III Top-Line Results	Ardelyx Inc.	tenapanor	Hyperphosphatemia	PHREEDOM; Met Primary Endpoint	2	71
Phase III Top-Line Results	Aldeyra Therapeutics, Inc.	reproxalap	Dry Eye Disease	RENEW; Mixed Results	0	55
Phase III Top-Line Results	Aurinia Pharmaceuticals Inc.	voclosporin	Lupus Nephritis	AURORA; Met Endpoints	0	62
Phase III Top-Line Results	Sage Therapeutics, Inc.	SAGE-217	Major Depressive Disorder	MOUNTAIN; Mixed Results	-13	48
Phase III Trial Initiation	Phathom Pharmaceuticals	vonoprazan (Takecab)	Erosive Esophagitis	PHALCON-EE; A Potassium Competitive Acid Blocker	59	59
Phase III Trial Initiation	Argenx NV/Halozyme	efgartigimod	Immune Thrombocytopenic Purpura	Double-Blind Study	39	62
Phase II/III Trial Initiation	Zealand Pharma A/S	dasiglucagon	Congenital Hyperinsulinism	In Pediatric Patients	0	68
Phase III Trial Announcement	Galectin Therapeutics, Inc.	belapectin	Non-Alcoholic Steatohepatitis	NASH-RX; Adaptive Design	0	13

Source: Biomedtracker | Informa, 2019

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More Top Level Pharma Exits In India As Cipla COO Departs

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It has been a year of high-profile pharma exits in India. And after the recent departure of Roche's India managing director, it's now Cipla Ltd.'s global chief operating officer, R Ananthanarayanan, who is moving on.

Ananthanarayanan (Ananth to his close peers) took charge as COO in August 2018, coming with a broad remit covering several key operational areas. His role included overseeing R&D, manufacturing, supply chain, the active pharmaceutical ingredients (API) business and the key geographies of North America, Europe and emerging markets. He had been tasked to help leverage and grow Cipla's generics portfolio and competencies in these markets.

Cipla confirmed to *Scrip* that Ananthanarayanan had decided to "pursue interests beyond the company," noting that the executive had been a key member of the company's leadership team.

"Our rich legacy of care and our humanitarian approach to business has made Cipla an employer of choice. As with any organization, our workforce continues to evolve to meet their personal and professional aspirations," Cipla said, adding that it valued both the "time Ananth spent" with the company as well as "his contribution."

Cipla did not, however, immediately clarify the specifics around the COO's exit or if a replacement had been identified, whether from within the ranks or external talent. Pharma in India has seen a number of recent top-level exits: Roche India managing director Lara Bezerra, Eisai Pharmaceuticals India Pvt. Ltd. head Sanjit Singh Lamba and Janssen India chief Sanjiv Navangul are among those who moved on this year.

RETHINKING MANUFACTURING

Cipla's Ananthanarayanan came with extensive industry experience; he was president and CEO of Teva API and Biologics from December 2014 to July 2018 and had also been president of the Pharmaceutical Services and Active Ingredients (PSAI) business and member of the management council at Dr. Reddy's Laboratories Ltd. in a previous stint. He has also held senior management positions at the Piramal group's pharma operations.

Ananthanarayanan, who holds a PhD in pharmaceutical technology from University of Mumbai, had been working on a string of new initiatives at Cipla in key areas such as manufacturing. In a previous interview with *Scrip*, the executive outlined how Cipla was rethinking and refining its manufacturing operations in the backdrop of an intensely competitive environment and evolving customer and regulatory requirements.

Cipla, he said at the time, was prioritizing several initiatives to ensure that its manufacturing keeps pace with the changing environment and demands in the sector, including looking at time to turn around a product and a continued focus on security and assurance of supply, among other areas.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Bruce Car	Agios Pharmaceuticals	Chief Scientific Officer	Bristol-Myers Squibb	Interim Head, Drug Discovery	6-Jan-20
Jonathan Biller	Agios Pharmaceuticals	Chief Legal Officer	Celgene Corp	Executive Vice President, General Counsel	3-Dec-19
Malin Carlsson	Alligator Bioscience AB	Chief Operating Officer	Ferring Pharmaceuticals	Vice President and Head, Translational Medicine	29-Nov-19
Curtis L. Ruegg	Amphivena Therapeutics Inc	Chief Executive Officer, President and Director	Parvus Therapeutics Inc	Chief Executive Officer and President	2-Dec-19
John Northcott	Nektar Therapeutics	Chief Commercial Officer and Senior Vice President	Pharmacyclics	Chief Commercial Officer	3-Dec-19
Dennis Urbaniak	Orexo AB	Executive Vice President, Digital Health	Havas Health & You	Chief Digital Officer	2-Dec-19
Andy Porter	Relay Therapeutics	Chief People Officer and Executive Vice President	Broad Institute	Chief People Officer	5-Nov-19

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

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