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Pfizer Eyes First-To-Market Opportunity In Alopecia

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Pfizer Inc. has an opportunity to be first-to-market with a drug for alopecia areata (AA), an autoimmune disease characterized by hair loss and often associated with psychological consequences. The company is advancing an oral Janus kinase (JAK) 3 inhibitor into a Phase IIb/III trial within months, now that the drug has shown a statistically significant efficacy benefit in a Phase IIa study.

The Phase IIa data mark a drug development breakthrough for treating AA, a disease in which immune cells attack healthy hair follicles for which there are no approved drugs. "There have not been any prior placebo-controlled studies in alopecia with oral kinase inhibitors or really any modern therapies," Senior VP and Chief Scientific Officer, Pfizer Inflammation and Immunology Michael Vincent said in an interview.

Pfizer tested two drugs in the Phase IIa trial versus placebo: the JAK3 inhibitor PF-06651600 and a tyrosine kinase (TYK) 2/JAK1 inhibitor PF-06700841. Both drugs significantly improved hair regrowth on the scalp relative to baseline, but while the TYK/JAK1 inhibitor appeared to have an efficacy advantage, Pfizer has decided to move forward with the JAK 3 inhibitor.

NOTABLE EFFICACY RESULTS

"Both drugs worked strikingly well," Vincent said. Although numerically, the TYK2/JAK1 inhibitor had an edge on several metrics, he said the totality of the data led the company to select the JAK3 inhibitor. "For this particular indication, the benefit/risk profile looked most favorable for the JAK3 program." The drug has been granted breakthrough therapy designation from FDA for AA.

The primary efficacy endpoint of the trial was improvement in hair regrowth on the scalp relative to baseline at week 24 as measured by the Severity of Alopecia Tool (SALT) score, a 100-point scale that is used as a standard measure for AA. Patients with partial and full loss of eyelash and eyebrow hair saw a significant improvement in hair regrowth. Other secondary endpoints and safety were also measured. The data were presented at the European Academy of Dermatology and Venereology meeting in Paris, France on Sept. 15.

The study enrolled 142 moderate to severe AA patients who were randomized to receive '600, '841 or placebo. Improvements in the SALT score at 24 weeks was 33.6 points and 49.5 points for the JAK3 and TYK2/JAK1, respectively. Some patients with complete hair loss saw 90% and 100% improvements, Vincent added. Patients also responded rapidly to treatment, with improvements occurring within four to six weeks.

Adverse event rates were comparable between treatment groups, with the most common adverse events being related to infections, gastrointestinal and skin/subcutaneous tissue categories.

The next phase of development will be a Phase IIb/III study that will incorporate some dose-ranging components. The Phase IIa trial was not a dose-finding study and was intended as an initial exploration of the potency of the drugs for AA. The JAK3 inhibitor is also in Phase II development for rheumatoid arthritis, Crohn's disease and ulcerative colitis.

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

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Adding Vascepa gives further benefits (p11)

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A leader in gene therapy (p8-9)

from the editor

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It's fascinating when a company explains its naming rationale. Antibody-drug conjugate specialist Glythera has announced it is marking its transition from a technology licensing firm to in-house clinical development by renaming itself Iksuda Therapeutics. The rather abstruse explanation for how the new name "signifies the company's transition" was that Iksuda meant "all conquering" in Sumerian and reflected the firm's aim to conquer ADC instability and create stable, effective ADCs to treat the most severe cancers. That sort of thinking is by no means atypical in the world of corporate identify forming, although sometimes the reasoning is more obvious.

Bausch Health Companies' recent renaming was clearly aimed at putting its unsavoury behavior under the Valeant brand firmly aside. Still, for the former ICN the name Valeant itself, like Iksuda, was once seen as bold and meaningful fresh branding.

Faux-Latin derivation like Valeant, Novartis and Aventis is more common than Sumerian, but other ancient cultures are freely plundered for biopharma's corporate nomenclature. Not that going back a long way for your reference always guarantees a safe choice. Ionis Pharmaceuticals used to be named after the Egyptian goddess of health Isis – until a homonymous terrorist group emerged.

A particularly intriguing case is that of Nephros Therapeutics. Back in the noughties it unveiled a new name which it said reflected its mission to extend the lives of patients with severely compromised kidney function. No matter that the first name seemed to serve that purpose passably already. Rather ingeniously, the new name had the virtue of also signifying "this company wasn't always called this". RenaMed Biologics, where are you now?

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Biosimilar Tipping Point: Five Questions For Henlius CEO
https://bit.ly/2zt5ht3
Now valued at close to $3bn, Henlius is one of the largest biotech unicorns in China. CEO Scott Liu sat down with Scrip in an exclusive interview to discuss biosimilar development in China, emerging market expansion plans, and its venture into immuno-oncology combo strategy.

Interview: DKSH Building Healthcare Services In Changing Asian Markets
https://bit.ly/2N2KaRC
Market expansion services provider has its headquarters in Switzerland but a long history and most of its business in Southeast Asia, where the global head of its Business Unit Healthcare tells Scrip it continues to build a broad range of services based around knowledge and penetration of local markets.

Merck & Co Needs To Go Low On Price For New HIV Drugs In EU
https://bit.ly/2O5tJsz
Pifeltro and Delstrigo have been backed for approval by the CHMP but how well they will fare on the market depends on a competitive pricing strategy and continuing to benefit from current European guidelines which recommend NNRTI-containing regimens for HIV.

Clinuvel Is Planning For US Commercialization Of Ultra-Orphan Drug Scenesse
https://bit.ly/2N3EerA
Clinuvel's Scenesse for the ultra-rare, light-induced disease erythropoietic protoporphyria (EPP) is already approved in Europe and the company is hopeful that a rolling NDA submission could pave the way for a US launch.

Finance Watch: Lilly Completes Elanco Animal Health Spin-Out As New IPO Filings Keep Rising
https://bit.ly/2pAz4Kn
Public Company Edition: Eli Lilly & Co. wasted no time spinning out its animal health business Elanco, which raised $1.5bn in its public debut. Also, as the biopharma IPO tally rises, Vivo Capital launches a new public life science company fund. Meanwhile, Concordia completes its recapitalization.

Asia Deal Watch: BIOCAD, Shanghai Pharma Agree On Pair Of Russian/Chinese Joint Ventures
https://bit.ly/2OWwvNG
The JVs will develop and commercialize therapeutics for multiple cancer types and autoimmune disorders in China. Novocure partners its Tumor Treating Fields technology with Zai Lab, while Fate and ONO will collaborate on off-the-shelf CAR-T therapies.

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Novo Nordisk Cuts 400 Jobs In R&D Reshuffle As It Broadens Its Horizons

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Novo Nordisk AS indicated in August that it planned to reduce its costs and invest in growth, and on Sept. 18 announced that it will cut 400 research and development jobs in Denmark and China to restructure its R&D organization with the goal of accelerating the expansion and diversification of its portfolio.

The Danish firm is under pressure to diversify its product mix as competition and drug pricing concerns in the US and elsewhere continue to squeeze earnings growth. *(Also see "With Novo Nordisk Dependent On GLP-1s, Even Perceived Price Pressures Can Hurt " - Scrip, 9 Aug, 2018.)* Novo said its R&D reshuffle will "enable increased investment in transformational biological and technological innovation within both core and new therapy areas," with a focus on rapid advancement of internal programs and an acceleration of business development activities.

CEO Lars Fruergaard Jorgensen dismissed reports that massive layoffs were planned when Novo reported second quarter earnings results on Aug. 8, but said at that time that the company would cut some local and regional costs while investing in programs that will drive revenue growth. *(Also see "Seeking Efficiencies, Novo Nordisk To Squeeze Costs, Boost Growth Drivers " - Scrip, 8 Aug, 2018.)* The R&D reorganization announced nearly six weeks later makes good on that cut-and-spend promise.

Novo said it will establish four Transformational Research Units this year in Denmark, the US and the UK as satellite R&D offices focused on the pursuit of novel treatment modalities and platform technologies in priority fields, such as cardio-metabolic and stem cell research.

The company also said it will significantly increase its investment in automation and digital capabilities, including artificial intelligence and machine learning, which should result in faster and more efficient lead molecule selection and development. It will also invest in integration of lab infrastructure and information technology systems to improve R&D efficiency.

> Its R&D reshuffle will 'enable increased investment in transformational biological and technological innovation within both core and new therapy areas.'

"Delivering on our ambition of achieving even higher levels of innovation across a broader and more diverse range of chronic diseases requires that we have the optimal future skill base and allocate resources to our priority areas," Novo Chief Scientific Officer Mads Krogsgaard Thomsen said in the company's announcement about the R&D reorganization and layoffs.

Jorgensen told *Scrip* earlier this year that the company remained on the hunt for substantial licensing and acquisition opportunities after losing out on the acquisition of **Ablynx NV** to **Sanofi**, with a focus on the rare disease space and indications adjacent to Novo's two main therapeutic areas of diabetes and hemophilia. To that end, the company's R&D reorganization will accelerate its identification and pursuit of new therapeutic approaches based on external collaborations by establishing a new business development unit in the US biopharmaceutical research hotbed of Cambridge, Mass.

Novo already has made several business development investments this year, including an agreement earlier this month with **Ossianix Inc.** for the development of therapies based on shark antibodies that can cross the blood-brain barrier in the treatment of diabetes and other metabolic diseases. *(Also see "Novo Nordisk Grabs Shark Antibody-Based CNS Delivery Technology From Ossianix" - Scrip, 4 Sep, 2018.)*

The company also is collaborating with **Evotec AG** under a deal announced in August on the development of small-molecule drugs that may treat co-morbidities associated with diabetes and obesity, including kidney and cardiovascular diseases as well as fatty liver diseases, such as non-alcoholic steatohepatitis (NASH). *(Also see "Evotec's CEO Explains Logic Behind Drug Discovery Pact With Novo Nordisk" - Scrip, 23 Aug, 2018.)*

Novo also agreed in August to invest as much as $800m in the acquisition of **Ziylo Ltd.** to access its technology for the development of glucose-responsive insulins. *(Also see "Novo Nordisk Makes Long-Term Bet On GBM Technology With Ziylo Buy" - Scrip, 17 Aug, 2018.)*

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Boehringer Ingelheim Is Getting Bets In Early In IO Space

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Boehringer Ingelheim GMBH prides itself on early-stage deal making but in some cases the groundwork has been done years in advance by the German company's venture capital arm.

"Our goal is to look at technologies which are very risky and adventurous in areas BI is not working on but where a strategic interest has been defined," Frank Kalkbrenner, head of the Boehringer Ingelheim Venture Fund (BIVF), told *Scrip* in an interview. This was certainly the case for immuno-oncology (IO).

The BIVF was set up in 2010 but the year before, when plans were being laid to set up the venture arm, the family-owned firm "already had quite an impressive pipeline" in cancer, he said. However, "it was all about small molecules, antibodies and the inhibition of certain pathways," such as BI's tyrosine kinase inhibitors that made it to the market, eg the lung cancer treatment *Gilotrif/Giotrif* (afatinib).

HEAVY INVESTMENT STARTED

However, "at that time it was already clear" from the early data coming out on **Merck & Co. Inc.** and **Bristol-Myers Squibb Co.**'s checkpoint inhibitors *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab) respectively, "that every cancer company needed to be in IO," Kalkbrenner said. BI "was not set up for it but the fund was," he declared, and it started investing heavily in the area.

Since 2010, BIVF, which at the beginning of this year more than doubled its fund from €100m to €250m, has made 13 investments in IO (it currently supervises a portfolio of 22 active companies). He said that the fund's work helps Jonathon Sedgwick, who heads up BI's recently established global research department dedicated to cancer immunology that is headquartered in Ridgefield, Connecticut "a chance to get a little bit of a head start" on rival pharma companies by identifying firms that may have technologies that could translate into therapies in four or five years' time. *(Also see "Boehringer's Expanded Venture Fund: Innovation First, Returns Second" - Scrip, 5 Jan, 2018.)*

INTERESTED IN TECHNOLOGY

One of the companies backed by the fund, Austrian oncolytic virus specialist **ViraTherapeutics GMBH**, was acquired last week by BI and it represents a good example of the way BIVF works, Kalkbrenner said. He noted that when the fund invested in the Innsbruck-headquartered biotech, there was no collaboration in place with BI , "we were just interested in the technology." On top of the financial contribution, he added that the company offers hands-on added value through its own extensive drug discovery, scientific and managerial expertise.

Kalkbrenner also stressed that when BIVF invests, "there are no strings attached and we don't have any preferred rights or cheap access" to the technologies being developed. It behaves like any other institutional investor and also needs to compete with the ventures arms of other pharma companies, he added.

However, Kalkbrenner noted that as well as working with institutional finance houses, BIVF is more than happy to co-invest with other pharma corporate venture players, citing relationships with the likes of **Takeda Pharmaceutical Co. Ltd.**, **Shire PLC**, **Merck KGaA** and **Eli Lilly & Co.** When asked whether those relationships can get strained when a portfolio company nears exit and a number of pharma partners are eyeing an acquisition, he said that "we play according to the rules of the market and if there are two or three corporate ventures involved, there might be competition but there also might be another that comes along around the corner offering better terms, a better price, a better future."

BI wants to be a partner of choice but "we can't acquire each and every company," Kalkbrenner added, noting that while "we have created half of the companies in our portfolio and been their first investors, we are still minority shareholders, so the majority may decide to go for another offer."

Price is not the only issue, he insisted, saying "don't underestimate the kind of relationship and trust you can generate" working with start-ups. The founders of a company "want to see their technology maturing into a product," Kalkbrenner stated and ViraTherapeutics, having worked closely with BIVF, decided BI "is the right home for their product."

The BIVF has also benefited financially from exits for portfolio companies that have been snapped up by other pharma players. High-profile cancer deals included the sale of T-cell based vaccines specialist Okairos, which was acquired by **GlaxoSmithKline PLC** in 2013, and **Rigontec GMBH**, which was sold to Merck & Co in September 2017. *(Also see "Rigontec Buy Adds RNA Tech To Merck & Co IO Portfolio" - Scrip, 6 Sep, 2017.)*

BUILDING A NETWORK

The sales of Okairos and Rigontec were financially attractive "but not the type of return our core business is delivering," Kalkbrenner noted, "so our real goal is to build our knowledge and our network – it is then up to our colleagues at BI whether they want to collaborate or acquire." *(Also see "BI's Business Development Focus Remains On Early Collaboration" - Scrip, 20 Jun, 2018.)*

As well as IO, BIVF has been increasing its focus on regenerative medicine, with six investments in the area. They include France's **Eyevensys SA**, a developer of a new non-viral gene therapy process to treat ocular illnesses, and **Acousia Therapeutics** of Germany, which is testing a new therapeutic approach to replace lost sensory hair cells by cellular regeneration and restore hearing.

Those two cases demonstrate the BIVF philosophy of going in early – investing in Acousia in 2012 and in Eyevensys in 2013 – and Kalkbrenner told *Scrip* that BIVF hopes to build a portfolio of 10-12 companies in regenerative medicine.

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Gilead's HCV Authorized Generics Effort Will Draw Market Share From AbbVie

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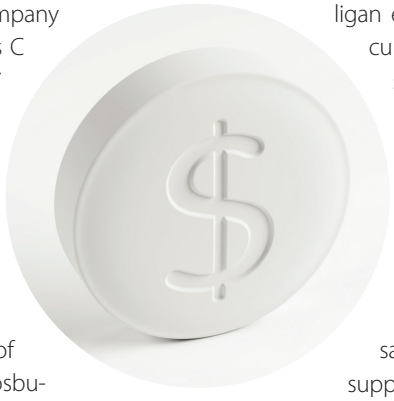

Gilead Sciences Inc.'s new spin-out company to sell authorized generics of its hepatitis C fixed-dose combination products *Harvoni* and *Epclusa* was packaged as offering potential out-of-pocket savings to patients – and it could do so – but the gambit should also draw market share away from **AbbVie Inc.** among US government-insured patients.

Foster City, Calif.-based Gilead announced Sept. 24 that it is launching the subsidiary **Asegua Therapeutics LLC** to sell authorized generics of Harvoni (sofosbuvir/ledipasvir) and Epclusa (sofosbuvir/velpatasvir), which will launch in January at a list price of $24,000 for 12 weeks of therapy.

Not only is this about 60% the list price for both of those drugs, but it also comes in below the $26,400 list price of AbbVie's *Mavyret* (glecaprevir/pibrentasvir) for an eight-week course of therapy. Mavyret holds a dominant share of US government-insured HCV patients, particularly among Medicaid patients, due to pricing differences.

In a same-day note, Morgan Stanley analyst Matthew Harrison called Gilead's decision "a solid lifecycle strategy" even if it is unlikely to significantly increase the specialty pharma's overall HCV revenue, which has been in sharp decline the past few years. Mavyret posted sales of $973m during the second quarter of 2018, up roughly 100% year-over-year, which placed AbbVie more or less even with Gilead for overall HCV sales, a sector Gilead dominated as recently as 2016.

"We do not expect today's news to grow Gilead's HCV revenues, but it could help to offset lower HCV volumes as Gilead takes back some market share from AbbVie," Harrison wrote. "We will wait to see if AbbVie is more aggressive with its government pricing based on today's news, which could counteract share gains by Gilead."

ABBVIE RESPONSE ANTICIPATED

ISI Evercore analyst Umer Raffat predicted in a Sept. 24 note that AbbVie was likely to respond to Gilead's announcement with some pricing change of its own for Mavyret. He estimates that Mavyret controls a 70% market share for US government-insured patients, including Medicare, Medicaid and the Veterans Affairs health care system.

"I doubt Gilead can make a move like this and [its] competitor won't respond," Raffat asserted. "It's possible that this starts another round of pricing flux in this market … which basically means that it's hard to take 2019 HCV estimates up … especially in the face of declining patient starts."

In Asegua and in the past, Gilead referenced the ongoing decline in US patient starts on HCV therapy as a reason why its revenues in that sector have tumbled. Pointing out that curing a disease gradually erodes the market for that disease's drugs, Gilead CEO John Milligan estimated that almost 1m Americans have been cured of chronic HCV infection on a Gilead product since the launch of *Sovaldi* (sofosbuvir) in 2013.

He argued that Gilead's HCV drugs effectively save the US health care system billions of dollars by forestalling patients' later liver health problems that could occur if their HCV went uncured, noting that the US health care system "is not structured to easily absorb the upfront cost of a one-time cure, even if it results in significant savings over a patient's lifetime." The complex drug supply chain in place in the US also creates a disconnect between a drug's list price and the price actually paid by insurers, Milligan added, although the savings realized by payers don't always benefit patients.

"In fact, in the past five years, the average price paid for our cures has decreased by more than 60% off of list prices after rebates paid to commercial and government health insurers," Milligan said in a statement posted concurrently with the Gilead news release. "However, because these rebates are confidential and are not required to be passed through to patients, these discounts effectively are invisible and do not always translate into lower costs for patients."

Gilead said the launch of the authorized generics of Epclusa and Harvoni – priced to "reflect discounts in the system today" – will give insurers the choice of offering the generics or the branded products. For Medicare Part D patients, getting the generics could save them up to $2,500 out-of-pocket over the course of therapy, the firm added. The generics also should create access to Gilead's HCV products for patients covered by state-managed Medicaid programs that have not offered Harvoni and Epclusa, it said.

Milligan said the effort also is an attempt to offer pricing transparency. "Over the past several months, we have searched for a viable path to reduce the list price of our branded HCV medications so that their cost to payers is more easily understood," he stated. "Unfortunately, existing contracts with insurers, together with laws associated with government pricing policies, make it unacceptably difficult to quickly lower the list price to reflect the discounted cost of our medicines."

Gilead previously has offered access to generic versions of its HCV and HIV drugs in developing nations, due at least partly to criticism it has taken for the prices it has set for its branded drugs. In 2014, it signed non-exclusive licensing agreements with seven India-based companies – since increased to 11 total – allowing them manufacture generic sofosbuvir and sofosbuvir/ledipasvir in 91 countries.

Last August, Gilead made additional concessions, reaching agreements to allow generics of its HCV and HIV drugs in four more countries – Malaysia, Thailand, Ukraine and Belarus.

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Viking's Liver Fat Reduction Data Portend A New Competitor In NASH

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Viking Therapeutics Inc. may have a heavy hitter on its hands if results from a small Phase II study of VK2809 stand up in larger studies – the novel, liver-selective thyroid receptor beta agonist yielded a 58% reduction in liver fat from baseline over 12 weeks, according to top-line data in patients with non-alcoholic fatty liver disease (NAFLD) reported Sept. 18. NAFLD is a precursor condition to non-alcoholic steatohepatitis (NASH).

VK2809 showed a statistically significant reduction in LDL cholesterol levels in the same study, suggesting both cardiovascular and hepatic health benefits.

The San Diego firm's stock finished the day up 87% at $19.46 per share, as at least one analyst pointed out that the data were numerically superior to widely praised Phase II liver fat reduction data in NASH patients that **Madrigal Pharmaceuticals Inc.** reported earlier in the year for MGL-3196. Madrigal's selective thyroid hormone receptor beta agonist showed a median 36% reduction in liver fat from baseline after 12 weeks of treatment in Phase II data released in December; Madrigal solidified those findings with 36-week histologic data from liver biopsies in May.

Viking did not release a full dataset on Sept. 18, because it hopes to present the larger picture at a late-breaker session of the American Association for the Study of Liver Disease conference Nov. 9-13 in San Francisco. However, it noted that NAFLD patients given 10 mg of its drug every other day (n=14) saw a 56.5% median reduction in liver fat from baseline at 12 weeks, while patients who received 10 mg daily (n=15) had a median 59.7% reduction at 12 weeks. That made for a composite median reduction of 58.1% in the 45-patient trial, compared to 8.9% for the trial's placebo arm (n=16).

"We are encouraged by the magnitude of liver fat reduction observed here, particularly at these low doses," Viking CEO Brian Lian said during a same-day investor call. "To our knowledge, this magnitude of liver fat reduction exceeds that reported for any other oral agent currently in development for NASH, though obviously no head-to-head studies have been conducted. We believe these results at these relatively modest doses support our view that VK2809's unique liver-targeting features provide differentiated benefit on this important measure of efficacy in NASH."

William Blair & Co. analyst Andy Hsieh pointed out that the Viking results appeared numerically superior to Madrigal's. "While we acknowledge all the caveats associated with cross-trial comparison, owing to the differences in enrollment criteria and patient baseline characteristics, we believe VK2809 achieved numerically better results than Madrigal's MGL-3196," he said in a Sept. 18 note, with a 57%-60% range in liver fat reduction in the Viking study compared to a 36%-42% range in the Madrigal trial.

Another potential differentiator between the two candidates, the analyst added, is the proportion of patients who achieved a clinically meaningful reduction in liver fat. Multiple studies have linked a liver fat reduction of at least 30% from baseline with greater likelihood of histologic response in NASH patients. Both Madrigal and Viking's 12-week data were based on a non-invasive measure: magnetic resonance imaging, proton density fat fraction (MRI-PDFF). Madrigal's 36-week data, however, were derived from liver biopsies, the gold standard for NASH diagnosis.

Viking reported that 76.9% of the patients receiving VK2809 every other day achieved a 30% reduction or greater in liver fat from baseline, while 90.9% in the daily dosing group hit that mark. For the placebo arm, 18.9% achieved at least a 30% reduction of liver fat from baseline.

In Madrigal's 116-patient Phase II trial, 60.3% of treatment arm patients (n=78) met the 30% or greater liver fat reduction mark, compared to 18.4% of control arm patients (n=38).

Lian also pointed out during the call that 62% dosed every other day and 73% dosed daily with study drug saw at least a 50% reduction in liver fat from baseline, for a composite 67% of treatment-arm patients who Viking termed "super responders." "While admittedly this is a little bit of our own invention, we nonetheless find it impressive that most patients who received VK2809 saw their liver fat content cut in half," the exec said.

Blair's Hsieh called VK2809's strong safety and tolerability profile, with no serious adverse events reported, an encouraging sign. Meanwhile, the drug actually showed reduced levels of the liver enzyme alanine aminotransferase (ALT) compared to placebo, which alleviated a prior concern for investors, Hsieh said. In a second note issued on Sept. 18, he increased his estimated US peak sales for the drug from $1.25bn to $1.71bn.

Given the its combined safety and efficacy profile in the Phase II study – including a significant reduction in LDL-C reduction, although numbers weren't given – Lian said VK2809 has a profile that might offer patients a range of health benefits.

"We believe the magnitude of the observed [liver fat reduction] effect suggests promising long-term benefits on histology in patients with NASH," he said. "In addition, treatment with VK2809 has been shown to improve patients' overall lipid profiles, with observed reductions in LDL, triglycerides and atherogenic proteins. We believe such results suggest potential benefits in cardiovascular health, an important consideration in the NASH population."

Biomedtracker concurred with the optimistic takes in its analysis, increasing the drug's likelihood of approval by seven percentage points to 27%, three percentage points above average for a Phase II NASH candidate. "The results of this study are very positive," Biomedtracker said, "with both primary and secondary endpoints reaching statistical significance and no serious adverse events reported for the duration of the trial, though the trial was small as it was only a Phase II study."

Lian said Viking's next steps are to compile the final dataset from the trial and complete animal toxicity studies of VX2809. The firm anticipates meeting with the US FDA in early 2019, after those tasks are completed, to determine what's next, which could be a biopsy data trial, the executive said.

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Amicus Makes Its Gene Therapy Move, Focusing On CNS Lysosomal Storage Disorders

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Amicus Therapeutics Inc. is poised to become a leader in gene therapy, with a focus on neurological lysosomal storage disorders (LSDs), via the acquisition of **Celenex**. The company announced the deal Sept. 20, which will add 10 gene therapy programs to the company's pipeline, including two in clinical-stage development for Batten disease, in exchange for $100m up front and milestones.

Privately held Celenex is progressing gene therapy programs developed from The Center for Gene Therapy at the Research Institute at Nationwide Children's Hospital and The Ohio State University.

The deal marks a big play for Amicus, which just recently got its first drug approved by the US FDA, an oral enzyme replacement therapy *Galafold* (migalastat), for the rare condition Fabry disease, after more than a decade of development. *(Also see "Amicus' Oral Fabry Drug Priced To Compete Against Traditional ERT" - Scrip, 13 Aug, 2018.)* The rare disease specialist's stock opened 8% higher at $12.76.

Amicus made the decision about a year ago to move into gene therapy, viewing the pioneering technology as pivotal to developing long-lasting cures for rare disease, and outlined the strategy to investors.

Gene therapy is increasingly viewed by the industry as an opportunity to cure some of the most serious genetic diseases, with early clinical successes beginning to stack up. The FDA approval last year of the first gene therapy in the US, **Spark Therapeutics Inc.**' *Luxturna* (voretigene neparvovec-rzyl) for a rare inherited blindness, brought the promise of gene therapy to the commercial market for the first time.

In prioritizing gene therapy business development, Amicus focused first on target disease areas, and eventually reached a list of 15 potential disease areas to pursue, with CNS disorders within LSDs a top priority. The company hired a new business development leader last year, Senior VP-Corporate and Business Development Michael Diem, who previously worked in business development at **Aevi Genomic Medicine Inc.**, **AstraZeneca PLC** and **GlaxoSmithKline PLC** in rare diseases.

> 'Celenex brought both a validated approach within gene therapy with this AAV9 approach, the expertise, but also this broad portfolio in one transaction.'

'THE WHOLE PACKAGE'

That process led Amicus to Celenex, in part because of the disease focus of the company and also because of the intrathecal delivery and AAV vector technology being developed, President Bradley Campbell said in an interview.

"One of the biggest areas of unmet need in the lysosomal storage disorder space are these CNS diseases, where traditionally they have been treated with enzyme replacement therapies, but it's very difficult to get enzyme replacement therapies into the brain, so there has always been this idea that a different approach – gene therapy perhaps – could be a way to meet that need," Campbell said.

The Celenex pipeline is based on an AAV9 gene therapy platform delivered intrathecally, through the spinal fluid, that has been clinically validated in other areas like spinal muscular atrophy (SMA). **AveXis Inc.**, recently acquired by **Novartis AG** for $8.7bn, has shown gene therapies based on AAV9 technology can cross the blood-brain barrier, making it an attractive method for CNS diseases.

"Celenex brought both a validated approach within gene therapy with this AAV9 approach, the expertise, but also this broad portfolio in one transaction, so we felt like it was really the whole package," Campbell said.

THREE CLINICAL-STAGE PROGRAMS

The two lead programs in the gene therapy portfolio that are in the clinic target different forms of Batten disease, CLN6 and CLN3. A third candidate, targeting Batten disease CLN8, will move into clinical development shortly. Amicus will now be the first company in the clinic with a gene therapy for Batten disease, a broad class of progressive fatal inherited disorders of the neuronal ceroid lipofuscinoses that generally effect children or adolescents. Each form is caused by a mutation in one of 13 different CLN genes, that leads to lysosomal dysfunction.

"While the onset of disease is variable across the different types and the speed of progression is different across the different types, some are more aggressive, and some are less aggressive, but they all end in the same place," Diem said.

CLN6 has an addressable patient population of about 1,000 worldwide, while CLN3 has the largest addressable patient population, about 5,000 patients worldwide, according to Amicus. The CLN6 program has enrolled 10 patients, who have received a single intrathecal administration; the company expects to add two more patients before completing enrollment in the coming months. Data from the trial are expected in 2019. The CLN3 program is just getting underway.

Amicus presented some preliminary data on two siblings treated with the gene therapy in the first clinical trial during a same-day call. Two years after administration, Hamburg motor and language scores indicate no disease progression in the younger sibling, who was 2.8 at the

time of administration, and disease progression in the older sibling, who was 5.3 years old, showed signs of stabilization. **BioMarin Pharmaceutical Inc.** relied on the Hamburg score for the successful development of the enzyme replacement therapy *Brineura* (cerliponase alfa) for CLN2 Batten disease, which was approved by the FDA in May 2017, based on a small, single-arm trial in 22 evaluable patients.

The preclinical programs at Celenex include gene therapies for other forms of Batten disease, Niemann Pick C, Wolman Disease, Tay Sachs and others.

Amicus said it would wait to see data from the ongoing clinical trial and consult with the FDA before speculating about regulatory requirements for approval or a potential timeline for a commercial launch.

BUILDING OUT IN GENE THERAPY

Celenex is a virtual company, so the integration should move smoothly into the current organization. The inventor of the technology, Celenex Co-founder Brian Kaspar, and investigator Kathrin Meyer, both of Nationwide Children's Hospital, will continue to work with Amicus to advance the treatments, according to Amicus.

"We will work very quickly to build out our own gene therapy team," Campbell said.

One issue crucial to gene therapy development is manufacturing. The three lead assets are currently manufactured at Nationwide Children's, which will continue to manufacture the clinical supply. But Amicus is also evaluating contract manufacturing groups for the lead programs and believes it will be imperative to develop manufacturing capabilities over the long term.

There are still a lot of development and regulatory hurdles for Amicus to get through before bringing its first gene therapy to market, but with what are expected to be high price tags for one-time gene therapies generally, anyone getting into the space needs to be thinking about payment models early on.

"As long as we are pricing for value and access, we think we can be accessible," Campbell said. "We've done tons of research with payers, physicians, providers." Plus, he said other new gene therapies are likely to help shape the gene therapy market before Amicus enters, which will help pave the way.

Amicus will finance the acquisition with a new $150m debt facility, which Campbell said will fund the upfront payment and the first several years of development costs. The company had roughly $550m in cash at the end of the second quarter, but wanted to keep a strong cash position, he said.

In addition to the $100m up front, Celenex shareholders are eligible to receive up to $15m in development milestones and $262m in regulatory and approval milestones across multiple programs. Amicus will pay no more than $75m in milestones over the next four years. Shareholders are eligible for up to $75m in tiered sales payments, but not royalties.

Published online 21 September 2018

CONTINUED FROM COVER

MORE TO LEARN ABOUT ALOPECIA AREATA

AA is an autoimmune disease that affects millions of people, though the prevalence is not well characterized, particularly for the moderate-to-severe patient population that Pfizer expects to target. The disease can affect people in their youth, with the main age of onset being 25 to 35 years old, and can result in depression and anxiety.

"We are doing some work to better understand this population," Vincent said. "It's not always just the extent of the disease that is impactful. Fundamentally, the impact on patients of this disease is predominantly psycho-social." The impact can also depend on the visible manifestation of the hair loss and the level of involvement. It can impact eyebrows and eyelashes.

Pfizer is looking at methods to collect data on some of the more social and psychological benefits of treatment. Pfizer measured various patient-reported outcomes in the Phase IIa trial, which it plans to report out at a future medical meeting, but Vincent noted that a validated patient-reported outcomes method for AA doesn't exist. The company is working to develop better validated tools to measure those kinds of outcomes. "At this time, the state of the instruments is not to the degree that you would see with many diseases that are studied," he added.

BUILDING A ROBUST PORTFOLIO

Pfizer has been a leader in the JAK space, with the 2012 FDA approval of *Xeljanz* (tofacitinib) for rheumatoid arthritis. Xeljanz, a JAK1/3 inhibitor, was the first JAK inhibitor on the market and has had a long monopoly in the space. It grew slowly into a blockbuster, despite slow uptake initially, gaining indications in psoriatic arthritis and ulcerative colitis more recently. *(Also see "Pfizer's Xeljanz: The Slow Road To Blockbuster Status" - Scrip, 4 May, 2017.)*

Now Pfizer is aiming to maintain its leadership position in the space with more selective JAK inhibitors, as rivals look to enter the market. **Eli Lilly & Co.**'s JAK1/2 inhibitor *Olumiant* (baricitinib) was approved by the FDA in June, but the agency only approved a lower dose of the drug that could present competitive challenges.

Other drug makers are also looking to get into the space, including **AbbVie Inc.** and **Gilead Sciences Inc.**

Pfizer has a whole portfolio of JAK inhibitors in clinical development in a range of indications. The company plans to continue development of '841 in psoriatic arthritis, Crohn's disease and ulcerative colitis. A selective JAK1 inhibitor is in Phase III trials for atopic dermatitis. In addition, the company is developing a TYK2 inhibitor for psoriatic arthritis and inflammatory bowel disease.

Bristol-Myers Squibb Co. is developing a TYK2 inhibitor in Phase III for psoriasis and got a lot of attention with positive Phase II data presented at the EADV Congress showing what it called "biologic-like efficacy" with a safe profile in patients with psoriasis. *(Also see "Bristol Engineers An Oral TYK2 Inhibitor With Biologic-Like Efficacy That Rivals JAK Safety" - Scrip, 12 Sep, 2018.)*

Pfizer's TYK2 inhibitor is in Phase I testing for psoriatic arthritis and inflammatory bowel disease.

As Pfizer looks to bring new drugs to market from its Inflammation and Immunology portfolio, Vincent said the company is focused on developing molecules that have unique selective profiles, which he says will bring unique benefit/risk profiles to the market.

"We feel we have as deep and as broad a pipeline in this area as anyone, if not better," Vincent said. "We think our history in this area positions us very well to make the best choices about how to target these selective agents to the best patient population."

Published online 18 September 2018

ICON CEO: CROs Must Be Aware Of Threat Posed By Big Tech

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ICON PLC, one of the industry's largest clinical research organizations (CRO) and the preferred provider of clinical research services for **Pfizer Inc.**, has felt the effects from ripples of biopharma consolidation, and the emergence of biotech, throughout its years as a services provider to the industry.

Its CEO, Steve Cutler, has seen much of this kind of activity play out first hand. Formerly working for Kendle as COO and latterly as CEO, he also spent 14 years working at **Quintiles Transnational Holdings Inc.** (now **IQVIA**) in project management. He also held several positions at **Sandoz International GMBH**. A native Australian, he represented his country 40 times on the rugby field between 1982 and 1991.

Despite his many years of experience in the clinical research sector, this straight-talking antipodean still loses sleep over potential disruption to the industry, specifically the threat posed by non-traditional players such as Apple, Google and Microsoft. "Those companies can apply significant technology and resources to the drug development conundrums and problems that we all face," he says.

"It's all very well to worry about it but you've got to say, 'Okay, how are they going to do it?' They can certainly bring a lot of resources, they could bring some innovative technologies. Whether that technology could fundamentally change the game and do it better, I don't know. Maybe they could," he wonders. "I think you've got to be aware of those potential threats. You've got to be open to those potential opportunities. Collaborate with those sorts of organizations because they've certainly been extremely successful in their space and, who knows, maybe they can bring a different way of looking at things to our business."

Certainly, if large tech providers do come knocking on the door of biopharma, Cutler will be ready to open the door. ICON inked a deal with Intel in April that enabled it to offer the Intel Pharma Analytics Platform for use in clinical trials. The platform is an artificial intelligence (AI) solution that enables remote monitoring and continuous capture of clinical data from study subjects using sensors and wearable devices, allowing it to quantify the impact of therapies. ICON has a number of existing technology and data partnerships with potentially disruptive entrants to the industry. Cutler says that ICON is "open to partnerships with all such organizations that can bring value and help solve some of our industry's key problems."

BEWARE THE BIOTECH BUBBLE

Where there is disruption there is also benefit, and vice versa. The funding of biotech projects within the last three to four years, for example, has been a boon to the clinical services industry with mid-size and large CROs feeling the benefits most of all.

However, when planning the long-term strategy of a services business, a customer operating within a funding bubble is not always the blessing it could appear to be. While the unprecedented amount of funding in the biotech space is a good thing for innovation, sustainability is also a huge factor to consider. "This industry is on a big wave at the moment but quite conceivably in a year or two, that could change," says Cutler. "And ultimately, in our industry, it's the large pharma companies who have the majority of the outsourcing and development dollar to spend." Pharma's largest 50 companies have approximately 75% of development dollars to spend, explains Cutler. "They are the ones who have a really sustainable pipeline, a portfolio of drugs, that are making money for them, so that they can reinvest in R&D."

ICON CEO Steve Cutler

The company reiterated this point at a recent investor day, and this is not a sentiment exclusive to ICON. "We have consistently heard this phrase from CROs – large and small, clinical and preclinical – and thought it worth emphasizing," said David Windley, managing director of Jefferies' Healthcare Equity Research team, in a recent investor note. "Our investor conversations suggest that observers view large partner discounts as driving lower margin. Because of the complexity of service delivered and idiosyncrasies of each client, repeat business drives process optimization and higher margin in the long-term." ICON's partnering strategy looks to customers with substantial budgets and opportunities for repeat business. "This strategy has borne mid-teens growth in its non-Pfizer business over the last year or so," says Windley.

"Biotechs are great when they've got their funding but many of them don't make a profit, and some don't even have revenue," Cutler says, "so, when they run out of money there's a problem. So, I think we all ride that wave and enjoy that wave while it's running. It's been running for a couple of years and long may it continue, but I think you've got to make sure you build your business on a long-term basis, and really, for us, that's the top 30 to 50 pharma companies in the world."

Traditionally, a biotech has one or two drugs, so a partnership with a CRO is not an focus for them. But increasingly these types of companies do want to stay with one service provider and execute the whole clinical program, rather than jumping from CRO to CRO. "It

may not necessarily be over many compounds or a large portfolio, but it's more of a one to one; you're the only provider, help us get to market" explains Cutler. "Biotechs want to be efficient with their spend and with their relationships, and not cast the net broadly over a large number of CROs. [They want to] go to one CRO for their program and the development work that they need to do. We've certainly seen a number of opportunities in that area."

Mid-size pharma companies are also starting to become more strategic in their partnering, says Cutler, explaining that this peer group has been much slower to partner up than large pharma. "They realize that they have to spend with fewer partners to make it really worthwhile for the partners to engage and to invest in that partnership. There is a maturation, if you like, in the mid-sized pharma sector around partnerships."

IMPACT OF CONSOLIDATION

With more companies looking to partner with services providers for the long-haul, they may not find as much choice as they would have done a few years ago. Consolidation has been the ongoing story of the CRO space for the past few years, with the largest seven CROs in the industry (IQVIA, **Parexel International Corp.**, **Pharmaceutical Product Development Inc.**, **Covance Inc.**, **PRA Health Sciences Inc.**, Syneos and ICON) engaged in some kind of M&A activity within the past 18 months.

The choices, and standards, are better for pharma, says Cutler, even though diversity in service providers is not what it once was. "It's still a highly fragmented industry and there are still 1,200 CROs around the world, but there are probably seven to 10 large ones who have the majority of the market share," he explains. "Typically, our industry doesn't pay dividends, we are still reinvesting the profits we make into our business in creative ways to improve what we do for customers. So, I think on the service side, it's about improving what we do and executing well."

There is a bifurcation in the CRO business, says Cutler. While there will always be a place for large and small CROs, it is the mid-size players, those that are making $100-400m in annual revenues, that are most at risk of being overlooked by potential customers. "They need to find their niche, they need to find their focus," he says. "There are pros and cons with any of the companies you work with and I don't think it will ever totally bifurcate but it is the companies in the middle that have to sort themselves out in the longer term. They are probably more at risk than the others."

CONSTANT PRESSURE

ICON made net revenues of $1.7bn in 2017. Its year-to-date revenues currently stand at $1.2bn according to its Q2 results, with full-year revenues expected to be in the range of $2.56bn to $2.64bn. The analyst John Kreger from William Blair estimates 2019 revenues to be around $2.8bn.

Despite the buoyant market for outsourcing that patently exists, the pressure to remain one step ahead of the competition is constant. "There's always pressure to be more efficient and effective, to be more innovative, creative, to deliver on time and budget. I don't know if that's necessarily increasing," explains Cutler. "In fact, you could argue with the amount of funding that's out there, there's a lot of opportunity. We are not all scrambling for the same dollars at the moment.

"I don't see any increasing pressure; I see constant pressure. As an organization, we must be constantly on our game to get better. You've got to get better every year; you've got to improve every year and you've got to drive your organization. If you don't get better, you're going backwards."

Published online 19 September 2018

'That's Huge, Folks:' Amarin's Vascepa Cuts CV Risk By 25% On Top Of Statins

MANDY JACKSON mandy.jackson@informausa.com

Superlatives were not in short supply when **Amarin Corp. PLC** reported a 25% reduction in cardiovascular risk in the REDUCE-IT outcomes trial for its triglyceride-lowering purified fish oil pill *Vascepa* (icosapent ethyl), exceeding the fairly low expectations for the long-term study.

"That's huge, folks," Amarin President and CEO John Thero said during an investor call on Sept. 24 when describing the "extremely exciting" 25% reduction in major cardiovascular events (MACE) relative to placebo ($p<0.001$). REDUCE-IT enrolled patients with LDL cholesterol maintained at healthy levels by statin therapy and with elevated triglyceride levels between 150 mg/dL and 499 mg/dL (median at baseline was 216 mg/dL). Amarin intends to submit a supplemental new drug application (sNDA) to the US FDA in early 2019 seeking a label change to reflect the REDUCE-IT results.

The cardiovascular outcomes trial (CVOT) vindicates the company, which asserted the CV prevention potential of Vascepa for several years, but could not win US FDA approval to treat the population studied in REDUCE-IT without results from the CVOT. Amarin even fought the FDA to defend its First Amendment right to free speech in talking about clinical trial results that were not included in the Vascepa label.

Amarin's sNDA will focus on statin-treated patients with triglyceride levels above 150 mg/dL and up to 499 mg/dL, which would expand Vascepa's treatable population beyond current labeling as an adjunct to diet to reduce elevated triglyceride levels in patients with severe hypertriglyceridemia (500 mg/dL or greater). *(Also see "Amarin granted nod to market fish oil pill" - Scrip, 27 Jul, 2012.)* REDUCE-IT enrolled 8,179 patients on statins with LDL-C between 41 mg/dL and 100 mg/dL (median of 75 mg/dL at baseline).

The FDA previously denied a similar label expansion based on the ANCHOR study, which found that Vascepa lowered both triglycerides and LDL-C in patients with less than severe hypertriglyceridemia. The agency followed an advisory committee determination that the triglyceride-lowering

CONTINUED ON PAGE 14

Scrip Awards Finalists

2018

www.scripawards.com

We are delighted to announce the shortlist for the 14th Annual Scrip Awards.

Over the summer, our panel of 17 respected judges has reviewed all the entries to produce a shortlist that displays the wealth of innovation, dedication and hard work that the pharmaceutical and biotech industries have shown over the past year.

The full range of industry activities from big pharma, biotech companies and CROs is represented: from novel deals, to new drug launches and finding technological breakthroughs in clinical trials. The Scrip Awards provides the industry with an opportunity to acknowledge its highest achievers across all parts of the value chain, and to recognize both corporate and individual achievement.

As in previous years, we will be announcing the winner of the Pharma Company of the Year Award (sponsored by CMIC) on the night, just as we do for the Lifetime Achievement Award (sponsored by ICON). We are thrilled that so many of you have taken the time to enter, and sorry that not everyone can make the shortlist.

This year's winners will be announced at a glittering black tie ceremony at the London Hilton on Park Lane on November 28.

Congratulations to all our finalists and good luck on the night!

For information on table bookings and sponsorship contact:

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- Neurocrine and AbbVie for elagolix in women's health
- Novartis and the University of Pennsylvania for CAR-T medications in pediatric cancer patients
- Roche and Ionis Pharmaceuticals to develop antisense drugs for Huntington's disease

FINANCING DEAL OF THE YEAR – PUBLIC
- Ablynx's $200m US IPO on NASDAQ
- Horizon Discovery Group's £80m public placing
- InflaRx's $100m IPO and secondary offering
- Morphosys' $239m overallotment issue and NASDAQ listing
- Polyphor's CHF165m IPO
- resTORbio's $163m Series A to IPO

FINANCING DEAL OF THE YEAR – PRIVATE
- AstraZeneca/MedImmune's $250m financing for spin-out Viela Bio
- BioNTech's $270m Series A financing
- Crescendo Biologics' $70m Series B financing
- Enterprise Therapeutics' £29m ($41m) Series B financing
- NodThera's £28m Series A financing
- PhoreMost's £11m ($15m) Series A financing

IQVIA'S CLINICAL ADVANCE OF THE YEAR AWARD
- Ablynx's Phase III HERCULES study of caplacizumab for acquired thrombotic thrombocytopenic purpura
- Alexion Pharmaceuticals' Phase III REGAIN study of Soliris (eculizumab) in myasthenia gravis
- bluebird bio's Northstar-2 study of LentiGlobin in beta-thalassemia
- GW Pharmaceuticals' Phase III GWPCARE4 trial of Epidiolex for refractory epilepsy
- Ipca Laboratories Phase IV study of hydroxychloroquine in type 2 diabetes mellitus in India
- Nanobiotix's Phase I/II trial of nanomedicine NBTXR3 in head and neck cancer

LICENSING DEAL OF THE YEAR – SPONSORED BY WORLDWIDE CLINICAL TRIALS
- AiCuris and Merck & Co (MSD) for Prevymis (letermovir) for cytomegalovirus
- AstraZeneca and Merck & Co (MSD) for Lynparza and selumetinib
- AstraZeneca and Pearl Therapeutics for PT027 in asthma
- Emergent BioSolutions and Valneva for the Zika vaccine candidate VLA1601
- F-star (through F-star Delta) and Merck KGaA for five bispecific antibodies in immuno-oncology
- Halozyme and Bristol-Myers Squibb for the use of ENHANZE drug delivery technology in immuno-oncology drugs

EXECUTIVE OF THE YEAR, FOR LARGE & MEDIUM CAP COMPANIES – SPONSORED BY LACHMAN CONSULTANTS
- Alan Hirzel, CEO of Abcam
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- Amy Schulman, CEO and co-founder of Lyndra
- Raman Singh, CEO of Mundipharma Singapore

WUXI APPTEC'S BIOTECH COMPANY OF THE YEAR AWARD
- AveXis
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- Diurnal Group
- F-star
- Genmab
- Neurocrine Biosciences

BUSINESS DEVELOPMENT TEAM OF THE YEAR – SPONSORED BY SKIPTA
- AstraZeneca and Avillion partnership team
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- CinnaGen's business development team
- Evotec's business development team
- F-star's business development team
- Rentschler Biopharma/Leukocare alliance business development team

SYNEOS HEALTH'S BEST NEW DRUG AWARD
- Kite Pharma/Gilead Sciences' Yescarta (axicabtagene ciloleucel)
- Novartis's Kymriah (tisagenlecleucel)
- Roche's Hemlibra (emicizumab)
- Spark Therapeutics' Luxturna (voretigene neparvovec-rzyl)
- TiGenix's Alofisel (darvadstrocel)

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CONTINUED FROM PAGE 11

effect was not proof enough that Vascepa could improve CV outcomes.

However, Amarin was careful to note that REDUCE-IT was designed to show that Vascepa could improve cardiovascular outcomes, not that reducing triglyceride levels causes a reduction in CV events. The company contends that its purified omega 3 fatty acid, which contains only eicosapentaenoic acid (EPA) and not docosahexaenoic acid (DHA), is effective due its EPA-only formulation. DHA-containing fish oil products have been shown to increase LDL-C.

REDUCE-IT RESULTS WOW INVESTORS, ANALYSTS

"The magnitude of MACE reduction is so far the greatest among all therapies on top of statins, far exceeding the clinically meaningful CV benefit expectation," Jefferies analyst Roger Song said in a Sept. 24 note.

Amarin's stock price more than quadrupled based on the REDUCE-IT results, rising from $2.99 at the end of the day on Sept. 21 to close up 314.7% at $12.40 on Sept. 24. Its market capitalization rose to $3.64bn from less than $1bn before the weekend. And Song predicted in a separate same-day note that the company's stock and market cap could rise further as investors – and potential buyers – come to appreciate the sales potential for Vascepa.

"We see meaningful potential for an M&A event given [Amarin] is significantly de-risked now, and shares are broadly under-owned by the market as the news has just hit and further developments are likely," he said.

To explain the significance of a 25% reduction in CV risk in REDUCE-IT, Song pointed out that cardiovascular risks were cut by about 15% in outcomes trials for the PCSK9 inhibitors *Repatha* (evolocumab) from **Amgen Inc.** and *Praluent* (alirocumab) from **Sanofi** and **Regeneron Pharmaceuticals Inc.**, and for the **Novartis AG** interleukin-1 beta inhibitor *Ilaris* (canakinumab).

Data from the FOURIER trial were added to Repatha's label in December. *(Also see "Outcomes Claim May Help Amgen Make Case For PCSK9 Inhibitor Repatha" - Scrip, 1 Dec, 2017.)* A supplemental biologic license application (sBLA) seeking a similar claim for Praluent based on the ODYSSEY Outcomes trial is under FDA review with an April 28 user fee date. *(Also see "PCSK9 Turning Point? Sanofi/Regeneron Dangle Lower Price Carrot For Praluent " - Scrip, 12 Mar, 2018.)*

Novartis' CANTOS study confirmed a CV benefit based on the anti-inflammatory effects of Ilaris in 2017. *(Also see "CANTOS: Modest CV And Intriguing Lung Cancer Benefit With Canakinumab" - Scrip, 27 Aug, 2017.)* Approved for various rare inflammatory conditions, Novartis is seeking approvals in the US and EU based on its effects on cardiovascular risk. *(Also see "Interview: Novartis Counts On AS and PsA For Cosentyx Growth" - Scrip, 15 Jun, 2018.)*

'Of course, it will be important to see details and an FDA review of the trial.'

Amarin notes that it does not compete with PCSK9 inhibitors, but it pointed to CVOT trials for Repatha, Praluent and other drugs tested on top of statins to show that no other add-on therapy has shown the same effect as Vascepa in REDUCE-IT. **Merck & Co. Inc.**'s cholesterol absorption inhibitor *Zetia* (ezetimibe) showed only a 6.4% reduction in cardiovascular risk in the IMPROVE-IT trial.

Also, **GlaxoSmithKline PLC**'s now-generic EPA- and DHA-containing omega 3 fatty acid pill *Lovaza* showed only a 3% CV risk reduction in the ASCEND trial. *(Also see "Teva generic fish oil pill win ruffles Amarin investors" - Scrip, 9 Apr, 2014.)* That drug was approved in 2004 with the same severe hypertriglyceridemia indication that Vascepa obtained in 2012.

However, Amarin has pointed to the JELIS study in Japan for the EPA-only fish oil product *Epadel*, which had a 19% reduction in CV risk. The company has said, and continues to note, that the JELIS result was a good indicator for REDUCE-IT.

"Top-line results from the REDUCE-IT study, with a relative risk reduction of 25% in MACE, were quite positive, and given the failure of other trials added on to statins that lower triglycerides/increase HDL-c, officials were right to tout their accomplishment," Biomedtracker wrote in its analysis of the top-line data. "Of course, it will be important to see details and an FDA review of the trial, but the substantial MACE reduction should help to offset issues that could come up if the benefit were more marginal."

Jefferies analyst Song noted that "our doc survey suggested 10%-15%+ risk reduction in MACE is considered clinically meaningful," and estimated that the 25% CV risk reduction in Amarin's outcomes study could add up to $2bn-$3bn in annual peak sales for Vascepa.

The company has been marketing its drug since 2013 without achieving the blockbuster potential promised for the past five years, but it has not changed its prior guidance of $230m in 2018 sales based on the REDUCE-It results. Amarin does not intend to provide updated guidance for 2018 and 2019 until its third quarter earnings call in November.

"We believe that the REDUCE-IT results position Vascepa to become a blockbuster, but we don't have enough data to provide guidance regarding the rate of near-term growth," CEO Thero said during Amarin's call. "We will revisit this topic after we have feedback from physicians regarding their understanding and reaction to the results of the REDUCE-IT study."

MORE DATA TO COME, BUT INCREASED USE IS ANTICIPATED

The company only reported top-line results on Sept. 24 for the primary endpoint, which was a reduction relative to placebo in a composite of the first occurrence of MACE; events included in the MACE assessment were CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or unstable angina requiring hospitalization.

The safety of Vascepa was consistent with omega-3 fatty acids and the drug's label, Amarin said, with adverse event (AE) and serious AE rates that were similar between the Vascepa and placebo arms of the study. The median follow-up for patients enrolled in the trial was 4.9 years.

More detailed safety and efficacy results – including data from some of REDUCE-IT's dozens of secondary, tertiary and exploratory endpoints – will be presented on Nov. 10 at the American Heart Association (AHA) annual meeting in Chicago.

Amarin is keeping detailed results under wraps to preserve its ability to publish the data in a peer-reviewed journal; the company is targeting a fourth quarter publication. However, the secondary endpoint results were described as "robust" and consistently positive.

The company began preparing for increased prescribing of Vascepa before the REDUCE-IT results were available, spending $10m to manufacture additional supplies of the drug. It also has been working with its three active pharmaceutical ingredient (API) suppliers "to increase their capacity, such that we believe that, for next year, they'll be in a position to be able to provide us supply that would be able to support well in excess of $1bn in revenues."

Amarin is sticking to previously disclosed plans to increase its sales team from 150 to 400 representatives, which will allow it to increase its number of targeted doctors from 20,000 to 40,000.

The company also will work with existing partners in ex-US markets and may enter into discussions with new partners to seek approvals and expand Vascepa access outside of the US. However, Amarin does not intend to seek a buyer for the company, Thero noted, despite the $8bn-plus valuation that Jefferies' Song said may be possible in an acquisition.

"We are not focused on selling the company, and we will not comment on any questions on that topic or speculation in that regard as a matter of policy," Thero noted before kicking off the Q&A portion of the investor call.

Amarin, working on its own in the US, already has negotiated favorable reimbursement for Vascepa with tier 2 coverage on many payers' formularies, which means that patients covered by commercial health plans may pay as little as $3 per month out of pocket for the drug. Its list price is $278.58 for a bottle of 120 capsules, which is a 90-day supply, and a price that the company describes as consistent with statins (on an inflation-adjusted basis) before they went generic.

"Vascepa is already viewed as a safe drug, an inexpensive drug and as a drug that already enjoys broad insurance coverage as it has been on the market for five years," Thero said.

He noted that more than 90% of patients covered by Medicare Part D plans and more than 80% on commercial plans have access to Vascepa.

Thero also said that while REDUCE-IT's results will cause the company to review its pricing for Vascepa, Amarin believes that the drug's potential "is more of a volume play than it is a pricing play."

He added: "And hopefully, managed care, patients, physicians will appreciate that this is an opportunity with a drug which is affordable. They'll appreciate the safety profile. They'll appreciate that the administration is oral. And oral maintenance is a very easy, well-placed add-on to statin therapy. And hopefully, this will become the first choice of physicians for cardiovascular preventive care beyond statin therapy."

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Mixed Results In AZ's DECLARE-TIMI 58 CV Trial Cloud Implications For Farxiga

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Top-line data from the Phase III DECLARE-TIMI 58 trial showed **AstraZeneca PLC**'s diabetes therapy *Farxiga* (dapagliflozin) to be effective in reducing cardiovascular death and hospitalization for heart failure. However, the trial didn't meet its efficacy objective of cutting major adverse cardiovascular events in a statistically significant way, prompting some analysts to say the data would have minimal if any impact on boosting physician demand for the SGLT-2 inhibitor.

Farxiga is the last of the first wave of sodium glucose cotransporter 2 inhibitors to show a cardiovascular benefit.

By showing it met the primary composite endpoint of a statistically significant reduction in hospitalization for heart failure or cardiovascular (CV) death in a broad patient population in its DECLARE-TIMI study, the UK pharma has added to the evidence that this is a class effect for these type 2 diabetes drugs, which reached the US market in 2013.

The DECLARE (Dapagliflozin Effect on Cardiovascular Events)-TIMI 58 trial, which also confirmed the safety profile of Farxiga, took place over five years across 33 countries and involved more than 17,000 adults with type 2 diabetes who have multiple CV risk factors or established CV disease.

Full results from the cardiovascular outcomes trial will be presented at the American Heart Association annual meeting on Nov. 10, AstraZeneca's global head of cardiovascular and metabolic diseases Ludovic Helfgott told *Scrip*.

"This package of clinically relevant data will certainly further accelerate the growth of this medicine, especially among GPs who have so far been the most cautious towards using SGLT-2s," Helfgott predicted in an interview, adding: "I'm sure that overall the data will be good for the class as well."

AstraZeneca said hitting only one of the two primary endpoints in DECLARE-TIMI 58 would not jeopardize its attempts with the FDA or the European Medicines Agency to seek a cardiovascular benefit label for Farxiga in treating diabetic patients. "We just needed to hit one of them," a spokesperson for the company said.

ANALYSTS VOICE UNCERTAINTY

Still, the MACE efficacy miss was a concern for some analysts.

BMO Capital Markets focused on the point, saying that Farxiga's failure to reach statistical significance for the co-primary efficacy endpoint of time to the first event of

the composite of CV death, myocardial infarction, or ischemic stroke, known as major adverse cardiovascular events, or MACEs, was a "negative."

"This is surprising because CV benefits appeared to be a class effect with SGLT2s. Given the mixed results, we don't expect a meaningful change for Farxiga's near-term prescription trends," BMO analysts said in a reaction note.

Datamonitor Analyst Cameron Findlater agreed, saying the DECLARE results would not significantly impact the near-term prescribing rates of Farxiga.

"I believe patients already taking Farxiga will maintain their use of the drug as long as their A1c levels remain adequately controlled and physicians familiar with the drug will continue to prescribe at their usual rates given the results did not display negative outcomes associated with use of Farxiga," Findlater told *Scrip*.

Still, Helfgott said he was confident that the DECLARE readout would further drive AstraZeneca's strategy of trying Farxiga in other diseases, so expanding into potential new markets, potential new indications in years to come.

Independent trials are now being conducted studying Farxiga in heart failure patients and separately in patients with renal kidney disease. The trials include people with and without diabetes.

He said "there is a growing body of evidence" that SGLT2 inhibitors not only improve the blood glucose level, but also show cardiovascular and renal protective effects irrespective of the reduction of blood glucose in patients with type 2 diabetes.

AstraZeneca has consequently launched two heart failure studies, one in reduced ejection fraction which will read out in 2019 and one in preserved ejection fraction, which only just started to recruit patients. Both will involve some 4,500 participants.

"We have also launched a similar, very connected [Farxiga] study in chronic kidney disease to see whether we're able to delay the progression of kidney disease," Helfgott said, readout for which is expected "beyond 2019." *Published online 24 September 2018*

Phase III Data Put Zealand's Dasiglucagon On Track, But Behind Others, For Hypoglycemia Rescue

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Positive Phase III results across the board for **Zealand Pharma AS**'s dasiglucagon as a ready-to-use prefilled syringe rescue medication for severe hypoclyemia put the drug on track for a US FDA filing in the second half of 2019, but far behind two competing products that are already under review – **Eli Lilly & Co.**'s needle-free nasal product AMG504-1 and **Xeris Pharmaceuticals Inc.**'s XeriSol glucagon autoinjector.

Dasiglucagon (glucagon analog stable in liquid formulation) will be delivered in Zealand's ready-to-use *HypoP*al autoinjector rescue pen. Severe hypoglycemia is associated with confusion, seizures and loss of consciousness, and currently available rescue products need to be mixed from powder form and administered by syringe, which is challenging for non-health professionals to use in emergency situations.

Zealand Pharma reported positive results for dasiglucagon on Sept. 18 from a Phase III study of 168 patients with type 1 diabetes, which will help pave the way for a filing in the second half of 2019 and launch in 2020. The Phase III study tested dasiglucagon in a staked-needle prefilled syringe. Zealand plans to run a smaller Phase III bridging trial soon of its HypoPal auto-injector with the prefilled syringe in 40 to 60 patients with type 1 diabetes and file an NDA for both products, that is the auto-injector and staked-needle prefilled syringe.

The primary endpoint of the study just reported was the time to plasma glucose recovery, defined as the first increase in plasma glucose of at least 20 mg/dL from baseline without the need for administration of rescue intravenous glucose.

Dasiglucagon was associated with a significantly faster response – the median was 10 minutes, which was superior to the placebo median of 40 minutes and faster than **Novo Nordisk AS**'s *GlucaGen*, a powder formulation that needs to be mixed, at 12 minutes.

In the study, GlucaGen was actually premixed prior to use by participants, so in the real-world setting, administration of GlucaGen would take longer, Adam Steensberg, Zealand's chief medical and development officer, explained during a Sept. 18 investor call.

WHERE RIVALS STAND

The news was positive, but the product is behind two late-stage rivals. Eli Lilly announced that it had filed its AMG504-1 (LY900018), an intranasal glucagon delivered in a ready-to-use device, in the US and Europe in the second quarter and is positioning the product as the first needle-free option. The company had acquired worldwide rights to the candidate from Locemia Solutions in 2015. *(Also see "Lilly Adds PhIII Intranasal Glucagon To Diabetes Arsenal" - Scrip, 13 Oct, 2015.)* Based on a 12-month standard review for a new molecular entity (NME), a decision by the US FDA is expected between April and July 2019 and a decision in Europe is expected between January and October 2019.

An NDA for Xeris Pharmaceuticals XeriSol glucagon, a ready-to-use prefilled syringe formulation in an autoinjector, also was filed with the FDA in the second quarter. Based on a 10-month standard review clock for a non-original NME, a decision is expected between February and April 2019.

ZEALAND TOUTS DASIGLUCAGON'S SPEED OF ONSET

Zealand Pharma believes its data show a competitive profile. In addition to satisfying the primary endpoint in the Phase III study, dasiglucagon performed well on key secondary endpoints. Zealand reported that 99% of subjects in the dasiglucagon arm recovered from insulin-induced hypoglycemia within 15 minutes after dosing, compared with 2% for placebo and 95% for Novo Nordisk's GlucaGen.

"With these results, we believe dasiglucagon could be the treatment with the fastest onset among those marketed and in development treatment options. Compared with other important safety and efficacy features, dasiglucagon represents what could be a significant improvement in rescue treatment for diabetes patients," CEO Britt Meelby Jensen said during the company's Sept. 18 call.

Dasiglucagon was also well-tolerated in the Phase III trial, with similar though numerically higher rates of nausea and vomiting as in the GlucaGen arm: 55% vs 53% and 23% vs 19%, respectively.

Prior to the Phase III data released Sept. 18, Zealand Pharma had reported a positive outcome in a Phase III safety study in type 1 diabetes patients – showing that compared to GlucaGen, dasiglucagon was not associated with treatment-induced or treatment-elevated anti-drug antibodies.

Morgan Stanley analyst Matthew Harrison said in a Sept. 18 note that the "speed of recovery suggests that dasiglucagon could have a strong profile once launched, especially considering that GlucaGen is a powder that needs to be reconstituted before injection while dasiglucagon is in a ready to use pen."

Biomedtracker analysts, however, advised that it is difficult to compare dasiglucagon to other new, more convenient hypoglycemia products because only limited data has been released and the endpoints have differed. Head-to-head studies are not available.

In Phase III, Xeris' XeriSol Glucagon demonstrated noninferiority to approved glucagon on an endpoint similar to the one used in dasiglucagon study, i.e., an increase to over 70 mg/dL or at least 20 mg/dL, but within 30 minutes, rather than 15 minutes, and at a slightly numerically lower rate vs. the comparator (97.4% versus 100). In another Phase III study, 100% of those on the test drug recovered within 30 minutes.

As for Lilly's AMG504-1 nasal glucagon, this candidate demonstrated 98.7% success vs. 100% for the injected comparator in increasing plasma glucose to at least 70 mg/dL or at least 20 mg/dL over 30 minutes in a Phase III study, Biomedtracker analysts noted. The mean time for success was 16 minutes for Lilly's product vs. 13 minutes for the injected comparator.

ZEALAND STRESSES IMPORTANCE OF PEDIATRIC USE

Zealand will soon start a Phase III trial in 40 pediatric diabetes patients down to the age of six, which is expected to complete in mid-2019.

"If this study comes out successful, we can ultimately reduce or fully prevent the need for major pancreatic surgery in these children," Steensberg said.

Of the rescue market today in the US, 40%-45% of rescue kits prescribed are prescribed to kids.

"So that represents a key market, which is also why it makes a lot of sense to do the pediatric trial before filing," Meelby Jensen said.

The company is also planning a Phase III study in children with the genetic mutation that causes congenital hyperinsulinism and developing the product for use in a dual-hormone artificial pancreas pump in partnership with the Boston, Mass. start-up Beta Bionics, which announced it raised $50m in a Series B financing round on Sept. 17. A Phase IIb study will be starting shortly. During Zealand's investor call, Meelby Jensen highlighted the potential for the market to grow. About six million diabetes patients in the US are on daily treatment with insulin and severe hypoglycemia is one of the most feared complications for patients and relatives, with an estimated 300,000 hospitalizations every year in US alone, the exec said.

It takes several minutes for a health professional to administer the old kits, but most people in emergency situations would not even know how to inject the products, Steensberg said.

Zealand estimates that the glucagon hypoglycemia rescue market is underpenetrated "due to the shortcomings of the current product, as well as lack of promotion for many decades." In the US, it is worth about $350m, $100m of that from hospital use.

"With new and better products that are easier to administer, we believe the rescue products will grow significantly and reach $1bn in the US alone by 2030," Meelby Jensen said.

ZEALAND NEEDS PARTNER, THE QUESTION IS WHEN

Execs said during Zealand's call that they realize they need bring a commercial partner on board to make sure the product will be broadly available to all the patients who need it, though it is prepared to take the drug through registration stages on its own. The timing of engaging with a partner – before or after the filing – is not overly critical, Meelby Jensen said.

The company's number one priority market is the US, given that this is "by far the biggest and highest value market today," the CEO said. Zealand Pharma is open to having one global partner or having regional partners – both setups could work, Meelby Jensen said.

At the end of the day, what is important is to maximize overall value and feel comfortable with a partner pushing the product in relevant markets, she added.

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Phase III Roxadustat ALPS Data Positive For New Class Of Anemia Therapies

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Japan's **Astellas Pharma Inc.** has announced positive top-line data from the ALPS Phase III study involving the use of the oral investigational agent, roxadustat, in patients with chronic kidney disease (CKD) and anemia not on dialysis, boding well for its use as a therapeutic option in the condition, and for its potential to displace the use of erythropoietin.

The ALPS study found roxadustat showed superiority in efficacy versus placebo in terms of hemoglobin (Hb) response rate in the first 24 weeks of therapy, a primary endpoint, and against a second primary endpoint, Hb change from baseline at weeks 28 to 52, Astellas reported on Sept. 20. The first endpoint is required for a US marketing approval submission, and the second for an EU submission.

SAFETY CLOSELY WATCHED

The adverse event profile in ALPS was consistent with that seen in previous clinical studies of roxadustat, Astellas added. That's a noteworthy finding as the cardiovascular safety of roxadustat is being closely watched, due to increases in cardiovascular events seen in the past with other erythropoiesis-stimulating agents (ESA). A pooled analysis of key cardiovascular events from roxadustat's clinical trials is expected in March 2019, analysts noted.

Astellas expects to file, in the second half of 2018, a marketing application in Japan for roxadustat to treat anemia associated with CKD in patients on dialysis, the company reported several months ago. Astellas and the product's originator, **FibroGen Inc.**, reported a fourth Japanese Phase III study in such patients in May 2018, showing roxadustat met its primary endpoint in patients with hemodialysis-dependent CKD and anemia, previously treated with recombinant human erythropoietin or darbepoetin alfa. FibroGen has also noted that a US NDA filing for roxadustat was on target for the first half of 2019.

Roxadustat is an oral inhibitor of hypoxia inducible factor-prolyl hydroxylase (HIF-PHI) activity, and is being developed by Astellas in collaboration with originator Fibrogen Inc. in patients with CKD, on and not on dialysis, and patients with myelodysplastic syndrome; Astellas has rights to roxadustat in Europe, Japan, the Commonwealth of Independent States (CIS), the Middle East and South Africa. FibroGen and **AstraZeneca PLC** are collaborating on the development and commercialization of roxadustat in the US, China and certain other markets.

> Roxadustat showed superiority in efficacy versus placebo in terms of hemoglobin (Hb) response rate in the first 24 weeks of therapy, a primary endpoint.

A recent report from Datamonitor Healthcare suggests that roxadustat could become a top-seller in the anemia associated with CKD market in 2021, with sales of $1.1bn in 2021, driven by convenience and safety, and despite competition from biosimilar versions of **Amgen Inc.**'s *Epogen* (epoetin alfa). Another potential advantage of this class of agent could be a reduced requirement for patients to be treated with intravenous iron.

A number of HIF-PHI compounds are taking part in a race to the market, including **Akebia Therapeutics Inc.**'s vadadustat, which is in Phase III for CKD-related anemia in both dialysis and non-dialysis patients, and **GlaxoSmithKline PLC**'s daprodustat (GSK1278863).

FIRST OF THREE

ALPS is the first of three global Phase III studies being conducted by Astellas, mainly in Europe and the Middle East, that has reported top-line results. A second study by Astellas in non-dialysis CKD patients, DOLOMITES (versus darbopoetin), has completed enrolment, and a data readout is planned for the fourth quarter of 2018. The third Phase III study, PYRENEES, in CKD patients on dialysis, is comparing roxadustat with epoetin-alfa or darbepoetin, and a data readout is expected in the third quarter of 2018. The studies are part of a broader global clinical program conducted by collaborators, and a Japan-focused series of Astellas clinical studies.

In the five largest EU markets, Astellas estimates that around 371,000 patients have stage 5 CKD, of which 291,000 have anemia; and 724,000 patients have stage 4 CKD of which 432,000 patients have anemia. CKD can also be a cause and consequence of cardiovascular disease. The prevalence of CKD is increasing and is said to affect more than 200 million patients worldwide, with anemia being a common complication, associated with significant morbidity and mortality.

Astellas also has a second HIF stabilizer, YM311/FG-2216, in Phase II development in the EU and Japan in collaboration with FibroGen.

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Galera Raises $150m To Take Lead Drug From Phase III To NDA Submission

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Galera Therapeutics Inc. raised $150m in private funding, including $70m in Series C venture capital and $80m from a royalty financing, to develop its lead drug candidate from Phase III through a US FDA filing for its first indication – the treatment of radiation-induced severe oral mucositis (SOM) in head and neck cancer patients. Additional SOM and cancer treatment indications also are being pursued.

Malvern, Penn.-based Galera is developing multiple small molecule dismutase mimetics, which mimic the activity of human superoxide dismutase enzymes. Lead candidate GC4419 is designed to reduce elevated levels of superoxide caused by radiation, which Galera CEO Mel Sorensen said is given to about 50% of cancer patients, by rapidly converting superoxide to hydrogen peroxide and oxygen.

The GC4419 mechanism of action appears to improve both oral mucositis and the efficacy of radiation therapy, which the company will continue to investigate with its newly raised capital.

DATA, BREAKTHROUGH DESIGNATION ATTRACTED INVESTORS

The life science investment firm Clarus led the financing with participation from other new Galera investors – Adage Capital Management, HBM Healthcare Investments, Nan Fung Life Sciences, RA Capital, Rock Springs Capital and Tekla Capital Management LLC – and existing investors, including Correlation Ventures, Galera Angels, New Enterprise Associates, Novartis Venture Fund, Novo Ventures and Sofinnova Ventures.

Sorensen explained in an interview with *Scrip* that Galera's two-part financing came about after the company began to report positive Phase IIb results for GC4419 in the treatment SOM in head and neck cancer patients in December, and after the FDA granted a breakthrough therapy designation for the drug in February, as planning was under way for a Phase III trial to support approval.

"There were several things we could have done during that time; we were approached by several investors and Clarus were the ones who presented this novel financing to us, which in the end we figured was maybe the best and the strongest way for the company to move forward," Sorensen said.

Galera previously raised $57m in Series B venture capital, including a final $15m addition to the round in December. The company officially launched in December 2012 with $11m in Series A cash. Sorensen noted that the $70m Series C was oversubscribed. Clarus, as the beneficiary of the royalty-based component of the recent financing, will earn a single-digit royalty from sales of GC4419 and a related drug candidate until the payout totals an undisclosed multiple of the $80m financing.

"We had lots of enthusiasm for the data and the technology and we're going to use these funds to bring [GC4419] through Phase III, which will start in the next quarter, and get [us] all the way to" a new drug application (NDA) submission to the FDA, he said. "The great thing about this raise is that it allows us to do this on our own without any other financing."

In terms of partnerships, the CEO said Galera is "always open to talking to people, but right now we are focused very much on keeping this and moving it ourselves all the way to an NDA."

HEAD AND NECK INITIALLY, PANCREATIC CANCER IN THE FUTURE

The breakthrough therapy designation for GC4419 applies to the reduction of the duration, incidence and severity of SOM caused by radiation with or without systemic therapy; in head and neck cancer, radiation plus cisplatin chemotherapy is the standard of care.

The drug also has a fast track designation for the reduction of severity and incidence of radiation- and chemotherapy-induced oral mucositis.

The breakthrough therapy designation was granted after Galera reported results from a 223-patient Phase IIb clinical trial in which the duration of SOM was reduced from 19 to 1.5 days (92%), the incidence of SOM through completion of radiation was reduced by 34%, and the severity dropped by 47% compared with placebo. *(Also see "Pipeline Watch: Phase III Starts For BL-8040, Trigriluzole, MIN-101" - Scrip, 22 Dec, 2017.)*

Sorensen said the royalty deal is an indicator of the enthusiasm for Galera's technology and its GC4419 data to date.

"You only see royalty deals when there is conviction on the investor's side that you have a very active agent and that the probability of success is extremely high given the previous results," he said. "The [Phase IIb] results were across multiple endpoints and very consistent with a nice dose response. All of this pointed in the same way as the previous pilot study."

Galera has preclinical data showing that GC4419's conversion of superoxide to hydrogen peroxide, which is selectively more toxic to tumor cells, can enhance radiation's effect on tumors – this appears to be particularly true when the mechanism is combined with stereotactic body radiation therapy (SBRT), which produces greater levels of superoxide. A Phase I/II trial is under way to test GC4419 in combination with SBRT in patients with locally advanced pancreatic cancer.

"We have a portfolio of compounds and superoxide plays a role in multiple pathologies," Sorensen said. "We approached the head and neck cancer population [first], because it's a clear and well-established unmet medical need; 70% of patients with the very good standard of care – radiation and cisplatin – have this severe and debilitating mucositis."

And since 50% of cancer patients receive radiation at some stage of their treatment, Galera hopes to improve the safety and tolerability as well as the efficacy of radiation therapy. The company also will pursue programs in radiation-induced esophagitis.

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ASLAN, Sosei Pipeline Assets Hit By Development Delays

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Two companies based in Asia have unveiled unexpected delays to the progress of key clinical-stage pipeline assets, and although analysts do not appear to be too concerned at this stage about the longer-term implications, the companies say there will be some impact and further updates are awaited as the events are analysed further.

Singapore-based **Aslan Pharmaceuticals Pte. Ltd.** said it expects to take around four months to review and implement a voluntary amendment to the protocol for an ongoing single-arm clinical trial in China for varlitinib, which in this case being assessed plus capecitabine in patients with advanced or metastatic biliary tract cancer (BTC).

The open-label study planned to enroll 68 patients with BTC who had progressed on at least one line of prior chemotherapy. However, based on a review of patients recruited to date and discussions with key investigators, it has now been agreed that a protocol amendment should be submitted to local regulatory authorities.

This follows a finding that patients enrolled into the Chinese second-line study appear to have performed significantly worse, prior to recruitment, in the first-line setting than those observed in published global studies. In the first 27 patients enrolled, the first line response rate was approximately 7% and progression-free survival (PFS) was 2.7 months.

In the 14 patients that received a six-week scan in the study, one partial response and six patients with stable disease were reported based on site assessment; for the same 14 patients in the first-line setting, there were two partial responses and four patients with stable disease.

In comparison, in the landmark Phase III ABC-02 study in BTC comparing cisplatin plus gemcitabine to gemcitabine alone (the current standard of care for first line treatment of patients with advanced BTC), the first-line response rate was 26% and PFS was eight months for patients on cisplatin plus gemcitabine.

Given this variation, ASLAN said it will now modify the China study protocol to set more stringent enrolment criteria and ensure appropriate stage patients are taken into the study, in order to better provide an accurate evaluation of varlitinib's efficacy.

ASLAN will continue to recruit patients into the study and provide a further update on timelines in early 2019; top-line data from the study looks likely to be delayed to 2019 from late 2018 originally.

GLOBAL STUDY STILL ON TRACK

Varlitinib, an oral, reversible small molecule pan-HER inhibitor, targets the human epidermal growth factor receptors HER1, HER2 and HER4, which are mutated or overexpressed in many tumors and can cause excessive proliferative activity and uncontrolled growth.

The molecule – Taipei and Nasdaq-listed ASLAN's lead asset – is currently being studied in gastric, biliary tract, breast and colorectal cancers, and has been granted orphan drug designation in the US for gastric cancer and cholangiocarcinoma (a sub-type of biliary tract cancer, accounting for around 60% of cases).

ASLAN stressed that its global pivotal study in second-line BTC, TREETOPP, remains unaffected and on track to complete patient enrollment in early 2019, during which top-line results are due. This placebo-controlled trial is comparing varlitinib and capecitabine with placebo and capecitabine, and would be used to support regulatory approval submissions globally, assuming positive results.

"We believe it [the China study] is now unlikely to read out materially before the randomized TREETOPP study, which is on track for 2019 data (primary completion in July 2019)," BTIG analyst Robert Hazlett said in a note.

ETHNIC INFLUENCE?

The company said it is working with biliary tract cancer experts in China to better understand the differences in disease outcomes.

Dr. Mark McHale, ASLAN's Chief Operating Officer, said: "Based on our team's experience developing drugs such as gefitinib and afatinib that showed differences in outcomes between US and Chinese patients, we have been monitoring the China study closely."

The early identification of significant differences in the Asian patients compared to historical studies enabled measures to ensure the Chinese study will provide an accurate evaluation of varlitinib's efficacy, he noted, adding that single-arm studies are "inherently prone to these risks".

In a note on the delay, Leerink Partners' analyst Dr. Jonathan Chang said that, "Overall, while we're positive on ASLN's [ASLAN] Asia focused development strategy and the experience of the management team, we want to see more clinical and mechanistic validation for varlitinib in a catalyst-rich 2H18/2019."

'SURPRISE' FINDING FOR SOSEI DEMENTIA CANDIDATE

In a separate pipeline development, Japan-based and -listed **Sosei Group Corp.** and license partner **Allergan PLC** have decided to voluntarily suspend all clinical development activities for HTL0018318, a selective small molecule muscarinic M1 receptor agonist in early development for dementia including Alzheimer' disease (AD) and dementia with Lewy bodies (DLB).

A "neoplastic, rare tumor" finding was observed in a single animal study in non-human primates using doses and durations exceeding those used clinically in humans to date, and is currently of unknown cause, Sosei said.

The companies are "undertaking a thorough investigation to identify the significance and cause of the safety finding and determine the next steps. Data from previous preclinical and clinical studies will be reviewed as part of the investigation."

Sosei and Allergan have also reported the safety finding to both the US FDA and Japan Pharmaceutical & Medical Devices Agency (PMDA), and other regulatory authorities in countries where studies that have been completed.

PHASE II DELAY

The finding and related investigations is expected to delay the start of planned Phase II studies in AD and DLB patients by at least six months, and Sosei said there would be a revenue impact next year given that it no longer expects a major milestone payment from

Allergan in 2019 relating to the progress of '18318 in the partnered Alzheimer's program.

The two companies said the decision to voluntarily suspend clinical development activities with HTL0018318 was taken as a precaution after the animal study, which was investigating different doses over a nine-month period. No serious safety findings have been observed in any species in other animal toxicology studies extending up to six months.

Dr. Tim Tasker, Chief Medical Officer of Sosei, said in a statement that: "We were very surprised to see these results given the safety profile HTL0018318 has exhibited across all previous animal and clinical studies. We have taken these steps in the best interests of patient safety, which is our number one priority."

The information so far suggests "that this is not an accumulation problem, which potentially points to some underlying mechanism related to long-term activation of the M1 receptor in non-human primates," Deutsche Bank analyst Joseph Cairns said in a note on the findings.

CLINICAL STUDIES UNDERWAY

HTL0018318 is in a Phase I trial in the US (sponsored by Allergan) and a Phase II study in Japan in patients with DLB, as a potential new symptomatic treatment for symptomatic cognitive impairment.

A further Phase Ib study in AD patients (sponsored by Sosei subsidiary **Heptares Therapeutics Ltd.**) has also completed its clinical phase in Europe, from which data are being analysed.

Muscarinic receptors are G protein-coupled receptors (GPCRs) found in multiple tissues, but attempts to develop drugs targeting the M1 and M4 receptors have been scuppered by side effects caused by the related activation of M2 and M3 receptors.

Selective M1 or M4 agonists with no M2 or M3 activation are therefore seen as much more promising, and, as a direct and selective M1 agonist, Sosei's hope is that '18318 will avoid the problems that led to a development halt for **Eli Lilly & Co.**'s xanomeline due to cardiovascular and gastro-intestinal side-effects.

Data so far for HTL0018318 from around 310 individuals in the US and Europe, including healthy volunteers and patients with mild/moderate disease, have shown it to be well tolerated with no serious adverse effects at the tested doses for up to 28 days.

Sosei stressed that it is hoping to continue the human clinical development program with HTL0018318 as soon as possible, and Tasker added that "We remain confident that this compound has the potential to deliver important benefits to patients with AD and DLB."

COST TREATMENT UNDER ALLIANCE

The costs associated with investigating the new safety finding are covered under the terms of Sosei's 2016 global R&D and commercialization agreement with Allergan, and Sosei said for the nine-month period to December 31, 2018 it is actually expecting R&D expenses to decline because of reduced external spending.

While the voluntary suspension does not automatically trigger impairment of assets or goodwill, Sosei will fully assess the financial impact of the voluntary suspension and make any adjustments to the carrying value of relevant assets in the current quarter ending September 30.

Sosei and Allergan entered the partnership in April 2016, under which Allergan licensed exclusive global rights to a broad portfolio of novel Sosei selective muscarinic receptor agonists (M1, M4 and dual M1/M4 agonists) in development for major neurological disorders including Alzheimer's.

A clinical program to assess the selective M4 agonist HTL0016878 in certain neurobehavioral symptoms of AD is also underway, and dual M1/M4 agonists with potential in both cognitive and neurobehavioral symptoms are also at the preclinical stage.

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From the editors of PharmAsia News.

Tildrakizumab Set For Europe Debut – Can It Make A Dent?

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Almirall SA's first biologic, *Ilumetri* (tildrakizumab), is set to roll out in Europe in the "next few weeks" starting with Germany, expanding the Spanish group's psoriasis portfolio in a segment that has some formidable competitors.

Ilumetri, an IL-23p19 inhibitor, has been approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy – it had received a CHMP positive opinion on July 27. Tildrakizumab, licensed from India's **Sun Pharmaceutical Industries Ltd.**, in July 2016, was approved earlier this year by the US FDA. *(Also see "Ilumya Becomes Sun's New Branded Specialty Drug Pillar" - Scrip, 21 Mar, 2018.)*

Its approval in Europe is based on positive results from the reSURFACE 1 and 2 programs – both pivotal Phase III clinical trials, which included 1,800-plus patients from over 200 clinical sites worldwide, and demonstrated that tildrakizumab has a high level of safety and efficacy.

Ilumetri joins Almirall's dimethyl fumarate (branded *Skilarence* in the EU) in the psoriasis segment and the company had earlier this year projected peak sales of both products to exceed €250m ($293m) in Europe. Psoriasis affects an estimated 7.8 million adults in this region and around 125 million people world over.

FORMIDABLE COMPETITION

But breaking into the competitive psoriasis market in Europe isn't likely to be easy, with Ilumetri expected to directly take on **Johnson & Johnson**'s first-in-class IL-23 blocker, *Tremfya* (guselkumab).

Tremfya has already had some important wins – the UK's National Institute for Health and Care Excellence (NICE) had in June published

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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

Selected clinical trial developments for the week 14-20 September 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Alnylam Pharmaceuticals Inc.	*Onpattro* (patisiran)	polyneuropathy of hATTR amyloidosis	APOLLO; *Circulation*, Sept. 14, 2018.
Boehringer Ingelheim	*Ofev* (nintedanib)	idiopathic pulmonary fibrosis	INPULSIS-ON; *The Lancet Respiratory Medicine*, Sept. 14, 2018.
Boehringer Ingelheim	*Ofev* (nintedanib)	idiopathic pulmonary fibrosis	INSTAGE; *NEJM*, Sept. 15, 2018.
Acacia Pharma Group PLC	*Barhemsys* (intravenous amisulpiride)	post-operative nausea and vomiting (PONV)	*Anesthesia & Analgesia*, online Aug. 22, 2018.
Insmed Inc.	*Arikayce* (amikacin) liposome inhalation	non-tuberculous mycobacterial lung disease	CONVERT; *American Journal of Respiratory and Critical Care Medicine*, Sept. 14, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Novo Nordisk	semaglutide, oral	diabetes, type 2, in Japan	PIONEER 10; effective and well tolerated.
Astellas/FibroGen Inc.	roxadustat	anemia in chronic kidney disease, non-dialysis	ALPS; met primary endpoint, well tolerated.
Zealand Pharma	dasiglucagon	hypoglycemia in diabetes	16137; primary and secondary endpoints achieved.
GlaxoSmithKline	*Nucala* (mepolizumab)	severe eosinophilic asthma	COSMEX; reduced exacerbations.
Braeburn/Camurus	CAM2038	chronic lower back pain	Met primary and secondary endpoints.
AstraZeneca PLC/ Kyowa Hakko Kirin	*Fasenra* (benralizumab)	severe eosinophilic asthma	BORA; long-term safety and efficacy confirmed.
UPDATED PHASE III RESULTS			
AstraZeneca PLC/ Kyowa Hakko Kirin	*Fasenra* (benralizumab)	eosinophilic asthma	CALIMA, SIROCCO; efficacy noted.
AstraZeneca PLC	PT-010 (budesonide/ glycopyrronium/formoterol)	chronic obstructive pulmonary disease (COPD)	KRONOS; effective and well tolerated.
AstraZeneca PLC	PT-008 (budesonide/ formoterol) MDI	COPD	telos; improved lung function.
Sanofi/Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilumab)	atopic dermatitis in adolescents	Improved disease symptoms.
AIT Therapeutics Inc.	nitric oxide	bronchiectasis in infants	NO-BRO; reduced hospital stay.
Sesen Bio Inc.	*Vicinium*, fusion protein	bladder cancer	VISTA; encouraging signs of efficacy.
PHASE III INITIATED			
Iterum Therapeutics Ltd.	sulopenem, iv and oral	complicated urinary tract and intra-abdominal infections	SURE 2, 3; for multi-drug resistant infections.
Erytech Pharma SA	ERY-ASP (eryaspase)	pancreatic cancer	TRYbeCA1; in second line disease.
Innovent Biologics Inc./Eli Lilly & Co.	sintilimab (IBI308)	non-small cell lung cancer	ORIENT-11; in advanced or recurrent disease in China.

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 21

positive guidance for Tremfya, implying that adults with moderate to severe plaque psoriasis can access guselkumab through the National Health Service (NHS) in England and Wales.

> CEO Peter Guenter said Ilumetri is a safe, easy to administer, targeted IL-23p19 inhibitor that provides 'durable efficacy and long-term safety'.

Germany's drug reimbursement body, the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA), has also endorsed guselkumab stating that it offered "substantial additional therapeutic benefits" compared to treatment with comparators for all patient populations assessed.

The prominent IL-17 inhibitors that Ilumetri goes up against include **Novartis AG**'s *Cosentyx* (secukinumab) and **Eli Lilly & Co.**'s *Taltz* (ixekizumab).

BENEFITS HIGHLIGHTED

Almirall's Sept. 18 statement on the European approval quoted CEO Peter Guenter as saying that Ilumetri is a safe, easy to administer, targeted IL-23p19 inhibitor that provides "durable efficacy and long-term safety". The CEO had earlier referred to tildrakizumab's favorable dosing frequency compared with Tremfya, while noting that treatments cannot be compared outside of head-to-head studies. Tildrakizumab's low frequency of injections is also expected to encourage adherence.

Partner Sun had, while acknowledging the head start that competition had in the US, recently noted how the overall profile of Ilumya (as it is branded in the US) in terms of its efficacy, "the lasting effect" that the product shows for patients, and the "very low incidence" of side effects, were clearly "huge positives" for the product.

These attributes were "creating an impact", both with physicians to whom the firm was talking to and KOLs "who understand the product intimately," as well as with payers in the US, Sun's CEO (North America) Abhay Gandhi said at the time of the Indian firm's Q1FY19 earnings call last month. *(Also see "It's No Cosentyx/Taltz But Ilumya Pleases Customers, Says Sun" - Scrip, 15 Aug, 2018.)*

Informa's Datamonitor Healthcare had, however, earlier forecast that tildrakizumab could capture up to only 0.4% of the patient share of all moderate and severe patients across the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK), with its use restricted to patients being treated by dermatologists.

Tildrakizumab, Datamonitor said in its April 2017 forecast, is expected to capture up to 4% of moderate and severe patients from Janssen's *Stelara* (ustekinumab) and Cosentyx across all markets.

Published online 19 September 2018

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Julie Eastland	BioClin Therapeutics Inc	Chief Financial Officer and Chief Business Officer	Cascadian Therapeutics	Chief Financial Officer and Chief Business Officer	18-Sep-18
Brian Culley	BioTime Inc	Chief Executive Officer	Mast Therapeutics	Chief Executive Officer	18-Sep-18
Shane Kovacs	BlueRock Therapeutics	Chief Business and Financial Officer	RBC Capital Markets	Managing Director, Head, Biotechnology Investment	20-Sep-18
Alok Sonig	Lupin Ltd	Chief Executive Officer, US Generics and Global Head, Generics R&D and Biosimilars	Dr. Reddy's	Chief Executive Officer, Developed Markets	18-Sep-18
Georg C. Terstappen	Oxstem Ltd	Chief Scientific Officer	GlaxoSmithKline	Head, Platform Technologies and Science	10-Sep-18
Meredith Manning	resTORbio Inc	Chief Commercial Officer	Shire plc	Vice President, Global Product Strategy Lead, Hemophilia	18-Sep-18
Laura Mei	Tarveda Therapeutics	Vice President, Clinical Operations	Alexion Pharmaceutical	Executive Director, Global Clinical Operations and Metabolic Franchise Head	12-Sep-18
Waladimir Hogenhuis	Ultragenyx Pharmaceuticals Inc	Chief Operating Officer	GlaxoSmithKline	Senior Vice President and General Manager, Specialty Franchise	28-Sep-18

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

Source: Medtrack | Informa, 2018

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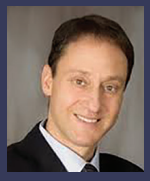
Jessica Morris, Co-founder, **OurBrainBank**, SVP and Partner at **FleishmanHillard**, *USA*



Professor Kenneth Getz, Director and Associate Professor at **CSDD**, **Tufts University School of Medicine**, *USA*

Inma Martinez, Venture Partner, Data Sciences & Product Innovation at **Deep Science Ventures**, *UK*

Daniel Prieto-Alhambra, Associate Professor & NIHR Clinician Scientist at **Oxford University**, *UK*

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