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Is Momenta's Biosimilar Exit A Bellwether For Industry Sentiment?

JESSICA MERRILL jessica.merrill@informa.com

Momenta Pharmaceuticals Inc. is exiting the biosimilar drug development space to redirect resources to novel pipeline drugs for immune-mediated diseases, in a move that could add fuel to growing concerns about a lackluster biosimilar market.

The decision, announced Oct. 1, comes after a lengthy strategic review process that started in January as the company sought and failed to find a buyer for its biosimilar business. Ultimately, the company determined it would terminate development of all but two late-stage programs, a biosimilar version of **AbbVie Inc.**'s mega-blockbuster *Humira* (adalimumab) and a biosimilar of **Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) in development in collaboration with **Mylan NV**. The company expects to end development of five other biosimilar programs in development with Mylan, including a biosimilar of **Bristol-Myers Squibb Co.**'s *Orencia* (abatacept).

The decision by Momenta, an early entrant in the complex generic space and later biosimilars, could add fuel to the debate about the commercial opportunity for biosimilars. Some other biosimilar manufacturers, and even FDA Commissioner Scott Gottlieb, have raised concerns about the commercial hurdles for biosimilars in the US that could stifle investment in biosimilar drug development. The number of biosimilar development programs in FDA's Biosimilar Biological Product Development Program dipped in the last months of 2017.

Momenta CEO Craig Wheeler talked to *Scrip* about the company's decision. He put some of the blame for Momenta fizzling out in biosimilars on the challenging dynamics in the category and some on company-specific issues, most notably the delayed launch of *Glatopa* 40 mg, a generic *Copaxone* (glatiramer) formulation, with partner **Sandoz International GMBH**. A manufacturing issue at **Pfizer Inc.**, the third-party manufacturer for the product, set the FDA approval of the drug back, ultimately allowing Mylan to get to market first with a 40 mg generic.

"We never had the chance to be the first generic in the marketplace," Wheeler said. "It took a tremendous amount of revenue out from underneath us."

Momenta ended up generating less revenues from its share of Glatopa 20 mg and 40 mg combined in the second quarter, just $11.8m, versus $19.1m in the year-ago period when only Glatopa 20 mg was available, because of the launch of Mylan's 40 mg product.

NOVEL DRUG INVESTMENT BEAT OUT BIOSIMILARS

"At the same time, the biosimilar business had become more challenging, mostly because of the patent delays that we were seeing in launching products," Wheeler added. For example, the company had originally forecast that a biosimilar version of Humira might launch in the US in 2017 and later readjusted the timeline to 2019. Now, after AbbVie has settled several patent infringement suits with biosimilar developers, it appears a

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

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South Korean Pharma
Plotting its own path to collaborative and open innovation (p21)

from the editor

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It was interesting to see last week that Danish parallel trading firm Abacus Medicine is planning to go public. The growth of high-priced medicines is providing rich pickings for intermediaries that can build a modest level of critical mass and deploy reasonably sophisticated IT systems to offer savings to customers: I wouldn't be surprised to see this segment of the pharma industry developing noticeably in size and ingenuity.

Price sensitivity is so pervasive, and you can see its influence in diverse geographies and therapeutic categories in just a week of coverage from our global team. From the margin pressures on biosimilars highlighted in our stories about Momenta's withdrawal from the space (cover story) and Pfizer's cut-price launch of copycat *Neupogen* (p4) to the need for Lilly to find a price point that will enable its next generation insulin to gain a meaningful place in the diabetes market (p7), pricing is often the make or break question. Even Roche's novel hemophilia A bleeding prophylactic has hit the US market at a very heavy discount to well established rival products (p9). Clearly, charging a premium for a premium new product is no longer a given.

On the other hand, justified excitement about the therapeutic breakthroughs being ushered in by advanced technologies including cell and gene therapies may be tempered by the pricing question, but it is not quenched (p5). It seems likely that innovative payment models that ensure patients can access such cures will crystallize, particularly when the costs of not providing access are high. The will is there, on all sides.

Scrip

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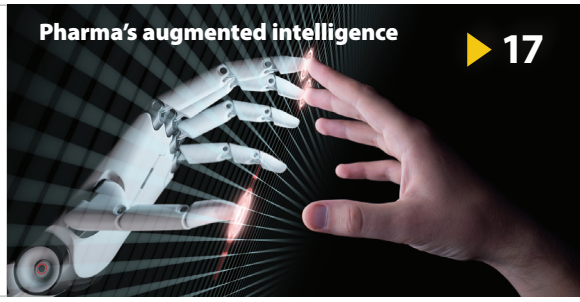

exclusive online content

Momenta Refocuses On Three Novel Autoimmune Drugs In Transition To More Traditional Biotech
https://bit.ly/2P7Yavw
Momenta will invest in three novel drugs and end development of all but two late-stage biosimilars under a new business strategy. The company is reducing its workforce by 50%, or about 110 employees.

Sarepta Commits To Rapid, Thorough Pivotal Study For DMD Gene Therapy Based On Functional Improvements
https://bit.ly/2RDYLq9
The company presented encouraging data on functional assessments of four boys treated with a micro-dystrophin gene therapy at the World Muscle Society, furthering momentum around the program.

Paratek's Antibiotic Nuzyra Survived 20 Years – Now For The US Launch
https://bit.ly/2ytBsGL
Company still mulling pricing for broad-spectrum antibiotic Nuzyra (omadacycline), which is set to launch in the US in the first quarter, following FDA approval Oct. 2.

Placebo Effect Or Just Bad News? Omeros Down On OMS721 IgA Nephropathy Data
https://bit.ly/2OgEWHm
Investors and analysts hope Omeros Corp can explain why its candidate drug for treating renal diseases performed only slightly better than placebo in tests on IgA nephropathy patients with high risk of progression, sending the biotech's shares sliding.

Deal Watch: Astellas/Cytokinetics Extend Partnership, Make Progress On SMA Candidate
https://bit.ly/2PnZH0p
The two firms hope improvement in the six-minute walk test might be accepted by the US FDA as registrational endpoint for reldesemtiv in spinal muscular atrophy. Blackstone acquires Clarus, while Merck licenses TriNKETs from Dragonfly.

Finance Watch: Government Grants Galore And Other New Funding Sources
https://bit.ly/2IKGCDg
While Forbion's new €360m venture capital fund and other investors have emerged to fund private and public companies, BARDA and other US agencies have been active supporters of biopharma firms in recent weeks. Also, KSQ grabs $80m in VC cash and VelosBios brings in $50m.

inside:

Pfizer Launches Nivestym At An Aggressive Discount To Other Filgrastim Products

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Pfizer Inc. is launching a biosimilar version of **Amgen Inc.**'s granulocyte colony stimulating factor *Neupogen* (filgrastim) in the US at an aggressive discount to the brand and other cheaper versions of the drug. The company announced its biosimilar *Nivestym* (filgrastim-aafi) is available on the market as of Oct. 1.

FILGRASTIM MARKET

Nivestym, approved by the FDA in July, joins a crowded filgrastim market that already includes two copycat products, so it makes sense that Pfizer would compete aggressively on price. The product will be priced at a wholesale acquisition cost of $350.40 for the 480 mcg prefilled syringe, a price that is 30.3% lower than the WAC of Neupogen, according to Pfizer.

The Nivestym price is also lower than WAC of **Sandoz International GMBH**'s biosimilar *Zarxio* (filgrastim-sndz) by about 20.3% and **Teva Pharmaceutical Industries Ltd.**'s follow-on product *Granix* (tbo-filgrastim) by 14.1%. Granix was approved through a traditional BLA pathway rather than the biosimilar pathway. The WAC price does not reflect the impact of rebates and discounts, so it is unclear how the prices stack up after discounts.

> Pfizer has learned some lessons from the disappointing launch of its first US biosimilar

The filgrastim biosimilar market has had more time to mature than some other biosimilar categories. Zarxio was the first biosimilar approved in the US, in 2015.

Granix was approved by FDA in 2012. Some payers, including the pharmacy benefit manager **Express Scripts Holding Co.**, have granted the products preferred formulary coverage over branded Neupogen. The category is one where biosimilars have had bigger impact than some other markets. Indeed, the alternatives have taken over the majority of the market share; Neupogen held only a 37% share of the filgrastim market at the end of the second quarter, according to Amgen.

The experience with filgrastim is different than what Pfizer has had with its first US biosimilar, *Inflectra* (infliximab-dyyb), a version of **Johnson & Johnson**'s *Remicade* (infliximab), which launched in 2016 with **Celltrion Inc.**. J&J has held onto roughly a 94% share of the infliximab market, despite the availability of two biosimilars, relying on a fierce rebating strategy. Pfizer is challenging J&J's rebating practices for Remicade in a lawsuit.

It seems Pfizer has learned some lessons from the disappointing launch of its first US biosimilar, however. The company launched Inflectra at a 15% discount to the wholesale acquisition cost of Remicade when it debuted in November 2016. Some payers at the time said the discount wasn't steep enough for what they were expecting biosimilars to deliver.

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CONTINUED FROM COVER

launch of biosimilar Humira will be delayed until 2023.

Momenta was looking to move several novel autoimmune disease drugs forward and needed to prioritize its investments. The novel drugs beat out the biosimilars.

UNANSWERED QUESTIONS

"We chose to reduce biosimilars as opposed to novel drugs, because the path to value creation on the novel drug side is clear," he said. "On the biosimilar side, with the continuing patent delays, nobody was ever sure when we were going to get to market, how many competitors were going to be in the market, and if there would be any real significant margin once we launched them."

Momenta launched a comprehensive process to sell the business, but ran up against a wall, because of the competitive dynamics. While there was a lot of interest, Wheeler said, most of the players in the space had portfolios that overlapped with the Momenta portfolio.

"What we did find was that there were not a lot of new companies looking to enter the biosimilar business," Wheeler said. "It kind of tells you that people are aware this is a competitive business, and the players that are going to succeed here are the larger generics players."

The company is in discussions with Mylan about next steps for the programs, which it has the right to exit under the 2016 collaboration agreement. The partners have not publicly disclosed the other programs in development. The two partnered in 2016, with Mylan paying $45m upfront to Momenta and agreeing to pay $200m in milestone fees; each company agreed to share equally in costs and profits. Mylan is responsible for commercializing the products under the deal.

But, Wheeler speculated, "they are exactly the kind of company that should be playing in [biosimilars]. They can play with a broad portfolio. They have the international footprint to take advantage of it."

CLINICAL PROGRAMS

While Mylan is committed to biosimilars with a deep pipeline of drugs in development, CEO Heather Bresch is one of the leaders who has expressed concern about the lack of commercial incentives in the market for biosimilars. The company also is in the midst of exploring strategic alternatives. Mylan declined to comment on the news from Momenta.

Momenta is now turning its attention to three clinical-stage programs for autoimmune diseases, and announced a restructuring that will eliminate 50% of the workforce or 110 employees, largely in biosimilar drug development.

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Cell And Gene Therapies Test New Waters In Pricing And Reimbursement

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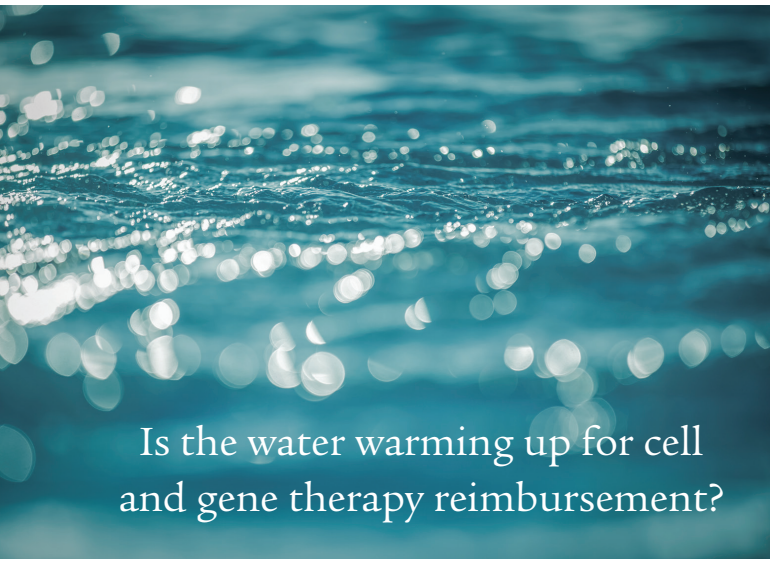
The regenerative medicine field finally has progressed to the commercialization stage, but the first cell and gene therapies are launching into markets that don't know how to pay for costly one-time treatments.



Companies with the first commercial products are testing new waters in pricing and reimbursement, negotiating novel agreements that ensure patients have access to treatment. Executives from companies with approved cell and gene therapies, and firms hoping to launch their own regenerative medicines soon, discussed the challenges and the potential to shape how these treatments are paid for during the annual Cell and Gene Meeting on the Mesa hosted by the Alliance for Regenerative Medicine (ARM) Oct. 3 and 4 in San Diego.

During a panel discussion about lessons learned by cell and gene therapy commercialization pioneers, Novartis Oncology Senior Vice President and Global Head-Cell and Gene Therapies Pascal Touchon described four lessons that **Novartis AG** has learned since the US launch of *Kymriah* (tisagenlecleucel) a year ago for relapsed or refractory acute lymphocytic leukemia (ALL) in children and young adults, and later for adults with relapsed or refractory large B-cell lymphoma.

Touchon said the first lesson is that it is possible to launch cell and gene therapies globally, but the second lesson is that it's "immensely challenging." The third lesson is that these medicines are transformative not just in terms of the treatment and survival of cancer patients, but for the stakeholders involved in access to chimeric antigen receptor T-cell (CAR-T) therapies, like Kymriah. And, for better or for worse, the fourth lesson is that this is just the beginning of figuring out how to pay for these products.

"We managed to work in a very collaborative way with payers – it's still going on now as we speak," Touchon said.

He noted that there already has been a lot of progress, though there still is a lot of progress to be made. But even in Europe, where single-payer government health care systems are particularly price-sensitive, agencies are seeing the value of CAR-T therapy for patients who've run out of options and may have an opportunity to significantly extend their lives beyond expected survival timelines.

Just a few days after European Medicines Agency (EMA) approval, Novartis reached an agreement with the National Health Service (NHS) in the UK under which the country's Cancer Drugs Fund will pay for Kymriah in its pediatric ALL indication, but not the adult lymphoma indication. *(Also see "Kymriah: England Becomes First In Europe To Say Yes To CAR-T" - Pink Sheet, 5 Sep, 2018.)*

"That shows how, if you engage early with payers, and you really educate them to show what is the value of these one-time, transformative therapies and you back that with strong cost-effectiveness data, that shows how effective are these therapies to also save cost in the system and create true cost effectiveness, then you can find ways," he added. *(Also see "Gilead And Novartis Unveil EU Marketing Plans For CAR-T Therapies, But Hurdles Remain" - Scrip, 28 Aug, 2018.)*

Pilar Pinilla-Dominguez, senior scientific advisor at the National Institute for Health Care Excellence (NICE), which makes recommendations on whether the UK should pay for new medicines, said during a separate panel on acceptance, uptake and affordability of cell and gene therapies that the country is unique in Europe in regard to providing access to CAR-T therapies.

Pinilla-Dominguez noted that the UK wants to make such treatments available to patients, so it encourages biopharmaceutical companies to engage with NICE early to help it understand the value cell and gene therapy therapies may bring before they're approved in the EU.

BIGGEST REIMBURSEMENT CHALLENGE: THE INFORMATION GAP

The concern about cell and gene therapies isn't just about the price – though it's at the heart of the problem of paying for these treatments – it's also about realizing the value of these medicines over the long term. While they may look like cures at 30 days, three months or even a year after treatment in a clinical trial, will patients' responses be maintained for several years or will an additional treatment be necessary in the future? If treatment effects are durable, however, curative treatments could wipe out high, recurring annual costs for treating chronic conditions.

Collaboratively negotiating agreements that offset the risk that cell and gene therapy results won't work or won't be long-lasting has been attractive to all types of payers, from government agencies to commercial health plans.

In the US in particular, commercial payers are concerned about the high upfront cost of a one-time therapy, which could cost $1m or more, because most patients will switch insurers before the return on investment is realized, since insurance providers are selected annually.

"There's a large disconnect between what health authorities want and what payers are going to need to actually reimburse a product,"

David Lennon, president of the Novartis-acquired gene therapy developer **AveXis Inc.**, said during the commercialization lessons-learned panel. "There's a lot of energy going into fast, rapid development, which leaves you with huge gaps when you go to have a conversation with payers about how to articulate the value of the medicine in their context."

That information gap is the biggest challenge in commercializing and winning reimbursement for cell and gene therapies, Lennon said. The potential 2019 approval for AveXis' lead product candidate AVXS-101 for spinal muscular atrophy (SMA) type 1, which will be submitted to the US FDA this year, will be based on a single-arm Phase I trial in which the comparator was a historical control.

"The reality is, a single center Phase I trial in one market – the US – is really a challenging dataset to take to a European or German payer, who really wants a much more robust package," Lennon said. Novartis plans to submit AVXS-101 to the EMA in the first half of 2019.

Pamela Keith, director of oncology reimbursement, access and value marketing at **Celgene Corp.**-acquired CAR-T therapy developer **Juno Therapeutics Inc.**, said during the panel on acceptance, uptake and affordability of cell and gene therapies that the information gap is why Juno has committed to publishing updates on its programs as the data matures, to show both physicians and payers how high response rates translate into improved outcomes. *(Also see "Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy" - Scrip, 22 Jan, 2018.)*

Like Touchon and Pinilla-Dominguez, Keith also noted that it is important to talk to payers early and often. While reimbursement discussions for oncology medicines typically start about 12 months before a drug's launch, she said Juno is initiating those talks 24-36 months before the launch of its CAR-T products via the ongoing sharing of clinical trial data.

NEGOTIATING FLEXIBLE, OUTCOMES-BASED DEALS

Lennon credited **Spark Therapeutics Inc.** for its efforts in resetting how payers think about the value these new medicines provide. Spark has been able to get payers to think about the cost of chronic therapy that's essentially eliminated by a curative gene therapy over five, 10 or even 20 years, which are long-term time horizons that payers typically do not consider in the evaluation of traditional pharmaceutical products.

Spark came in under the expected $1m price tag for its gene therapy *Luxturna* (voretigene neparvovec-rzyl) for patients with biallelic RPE65 mutation-associated retinal dystrophy, a rare inherited form of blindness with a few thousand patients in the US. Luxturna's list price is $850,000 for the treatment of both eyes, but Spark's reimbursement strategy includes discounts tied to patient outcomes at 30-90 days and 30 months post-treatment. *(Also see "Spark's Luxturna Approval Ushers In A New Gene Therapy Era" - Scrip, 19 Dec, 2017.)*

"We were fortunate in having Luxturna with an extremely strong regulatory package and the data that allowed us to do things that were a little different, at least in the United States," Spark Senior Vice President and Global Commercial Head Ron Philip said during the panel discussion about commercial cell and gene therapy pioneers.

As a result of Spark's flexible outcomes-based contracting arrangements, Philip said about 80% of commercial plans in the US have agreed to cover the cost of Luxturna. The one thing he said he would change, however, is to talk to the Centers for Medicare and Medicare Services (CMS) earlier about setting up a demonstration project rather than beginning that conversation around the time Luxturna launched, since government payers need more time to examine the potential benefits of gene therapy.

As a result of Spark's flexible outcomes-based contracting arrangements, Philip said about 80% of commercial plans in the US have agreed to cover the cost of Luxturna

Without long-term data for cell and gene therapies to show that the high upfront costs are justified by long-term value for patients and payers, outcomes-based contracting appears to be the way forward, but each agreement with each payer will have different terms and varying definitions of value.

Novartis also has been negotiating outcomes-based and indication-based agreements with payers for Kymriah, which launched at $475,000 for the one-time treatment of pediatric and young adult ALL patients. *(Also see "Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval" - , 31 Aug, 2017.)*

The company initially discussed such arrangements with CMS, but while CMS has expressed interest in these types of contracts and other arrangements, such as bundled payments to hospitals for administering CAR-T therapies and associated care, the payer's agreement with Novartis for outcomes-based Kymriah reimbursement has since been cancelled. *(Also see "CMS' Verma Touts Value-Based Payments After Cancellation Of Pilot For Novartis' Kymriah " - Pink Sheet, 12 Jul, 2018.)*

SPREADING OUT COSTS OVER MORE YEARS, MULTIPLE PAYERS

Other ideas for covering the cost of cell and gene therapies include amortized payments, where a payer may pay for the one-time treatment over a couple of years. High-risk pools also may be established in which multiple health plans and pharmacy benefit managers (PBMs) pay into a dedicated fund that covers the cost of high-priced therapies, spreading the risk across all of the participating payers so that one entity does not take a big hit when a $1m treatment doesn't work.

A high-risk pool is "one viable solution," Richard Powell, chief medical officer at Medpoint Management, said during the panel on acceptance, uptake and affordability. Medpoint provides managed care management services for independent health care providers.

Pools may be especially attractive to US commercial payers to deal with the problem of patient "portability" among health plans, Powell said. In California, he noted, patients stay with a health plan for less than a year, on average, so amortizing the price of a cell or gene therapy over three or five years means that payers would continue to reimburse the cost of a one-time treatment long after the patient has moved on to another health insurer.

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Lilly's Ultra Rapid Lispro Mealtime Insulin Sails Through Phase III, But Will It Be Enough?

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Positive topline data from **Eli Lilly & Co.**'s two Phase III PRONTO studies bring its Ultra Rapid Lispro mealtime insulin – its *Humalog* successor – a step closer to the market for type 1 and type 2 diabetes, though questions remain about differentiation and justification for branded pricing in the future.

Standard treatment for diabetic patients who need insulin begins with a longer-acting insulin to manage a patient's baseline blood glucose, and then mealtime insulin is added to manage blood sugar spikes as needed.

Compared with marketed products, new faster-acting products promise to give patients more convenience in terms of when they need to inject with insulin around meal times. Lilly's Ultra Rapid Lispro (URLi, LY900014) is a formulation containing citrate and treprostinil as excipients to accelerate insulin lispro absorption.

Introduction of faster, better versions of their insulin products is a prime way that sponsors are dealing with challenges to their diabetes franchises. Lilly's mealtime insulin Humalog (insulin lispro) brought in sales of $1.72bn in the US and $2.87bn globally in 2017. But **Sanofi** launched a Humalog copycat called *Admelog* this year, offering the same competition as a biosimilar, although it used the US FDA's 505(b)2 pathway.

On Oct. 2, Eli Lilly announced positive data from its Phase III studies showing that on top of a background of long-acting insulin, Ultra Rapid Lispro insulin met the primary efficacy endpoint of non-inferior hemoglobin A1C reduction at 26 weeks from baseline compared to Humalog in PRONTO-T1D and PRONTO-T2D, which enrolled a total of 1,895 people with type 1 and type 2 diabetes. Overall safety and tolerability were similar to Humalog in both studies.

After the primary efficacy endpoint of noninferiority was achieved, investigators analyzed one- and two-hour post-prandial glucose and hemoglobin A1c results for superiority.

Introduction of faster, better versions of their insulin products is a prime way that sponsors are dealing with challenges to their diabetes franchises

Lilly explained that in both studies, "URLi demonstrated superior reduction in glucose excursions at both one and two hours during a meal test."

"The studies showed no significant difference in severe, nocturnal or overall hypoglycemia rates reported by study participants," Lilly added.

Biomedtracker analysts said that meeting noninferiority criteria in both type 1 and type 2 studies, with an advantage on glucose excursions early on and no increase in hypoglycemia, is positive, but more details are needed to better understand the profile of the ultra-rapid insulin, as well as differences when administered at different times in type 1 diabetes patients.

"Since A1C was only non-inferior, did the drug have a benefit early on, but it was just not large enough to translate into superior A1c? Or did it have a disadvantage later on, that counteracted its initial benefit?" the analysts asked.

More details also are needed regarding whether hypoglycemia rates differed early on when LY900014 improved glycemic excursions, Biomedtracker analysts said. Lilly intends to present additional results in 2019 and file for regulatory approval next year.

PRICING WILL BE KEY FOR COMPETING

It's also unclear how new fast-acting mealtime insulins will be received in the market – that is likely to come down to pricing strategy.

Lilly said that URLi "was developed to help better control blood glucose levels after meals by more closely mirroring the way insulin works in people without diabetes," and that it will be a new option for mealtime insulin for keeping blood sugar in range after eating.

Novo Nordisk AS's *Fiasp* fast-acting version of its mealtime product *NovoLog/NovoRapid* (insulin aspart) is on the market following FDA approval in September 2017. Novo said in its second quarter earnings report that Fiasp brought in sales of DKK220m ($34m) in the first half of 2018 and noted that the drug has been launched in 18 countries.

The FDA label for Fiasp notes that it is non-inferior in terms of A1c in type 1 diabetes patients, though it does show a slight advantage for the product when given at mealtime, with the 95% confidence interval suggesting superiority, Biomedtracker analysts noted.

"The FDA did not want to grant a claim for superiority as this was not seen in the type 2 study and was not included in the statistical testing hierarchy to control for error. The difference (0.15%) was also not what would generally be considered that clinically meaningful. Nevertheless, it will be interesting to see whether LY900014 also had a nominal advantage in these patients," Biomedtracker analysts said.

With only slight potential advantages in some types of patients, the ultra-rapid insulins will likely still need to compete on price to be more widely successful, Biomedtracker analysts concluded.

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'Impressive' HbA1c And Weight Reductions Spur Phase III Plans For Lilly's Dual Incretin Agonist

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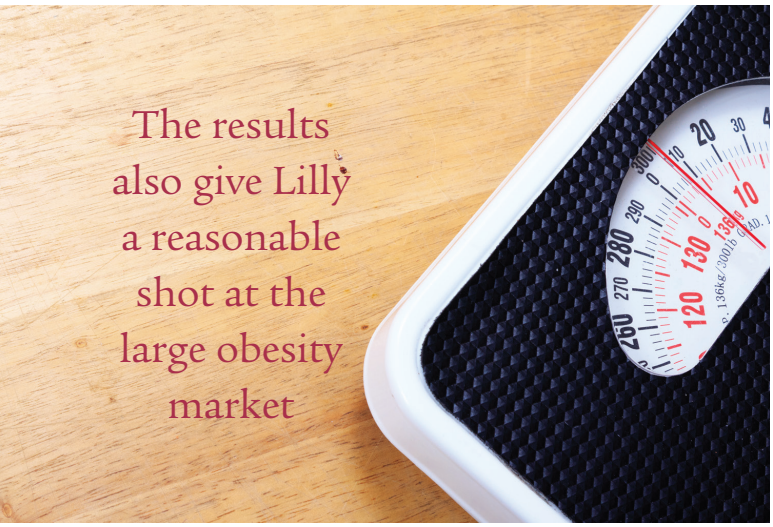
Eli Lilly & Co. is moving ahead quickly with LY3298176, a dual agonist of two incretins which has shown strong beneficial effects on HbA1c and body weight in a Phase IIb study in type 2 diabetics, and expects to start Phase III studies in type 2 diabetes "no later than early 2019". If successful, the investigational compound could be a significant competitor to GLP-1 agonists such as **Novo Nordisk AS**'s semaglutide in the condition.

Lilly is also evaluating next steps for the evaluation of dual GIP/GLP-1 receptor agonists like LY-3298176 in the treatment of obesity and for other conditions, the company announced on Oct. 4, following the presentation of the Phase IIb LY3298176 results at the annual meeting of the European Association for the Study of Diabetes (EASD), in Berlin, and their publication in *The Lancet* online on the same day.



Lilly's shares rose by 4.8% initially on Oct. 4, while those of rival Novo dipped, as investors digested these results, and also the full results from the Phase III EASE program evaluating the effect of the company's marketed type 2 diabetes drug, *Jardiance* (empagliflozin) as an adjunct to insulin in patients with type 1 diabetes, also presented at the EASD meeting.

Lilly is in an alliance with **Boehringer Ingelheim GMBH** on the development and commercialization of empagliflozin, and the companies said they had initiated regulatory discussions on gaining an additional indication for empagliflozin as an adjunct to insulin in patients with type 1 diabetes. *(Also see "Jardiance Is The Star Of Boehringer's Show, But Micardis Drag Spoils The Party" - Scrip, 2 Aug, 2018.)*

GLUCAGON SUPERFAMILY

Incretins are metabolic hormones, part of the glucagon superfamily, released after eating to help regulate blood sugar levels, and the lead investigator of the LY3298176 Phase IIb study, Juan Frias of the National Research Institute in California, US, said the results of the study were "unprecedented". After six months of treatment with LY3298176, average HbA1c reductions of up to 2.4 percentage points, and an average weight reduction of up to 11.3 kg (12.7%) were observed, the study found.

Jeff Emmick, vice president of product development at Lilly Diabetes, said the results "exceeded our expectations". The safety and efficacy of LY3298176 is to be assessed in the Phase III SURPASS program, with studies in type 2 diabetes expected to be completed in late 2021, the company said.

Analysts at BMO Capital Markets noted the LY3298176 results should strengthen Lilly's position in the rapidly-growing GLP-1 market versus Novo Nordisk's semaglutide franchise, and even generic GLP-1s later on. The results also give Lilly a reasonable shot at the large obesity market, the analysts added. *(Also see "With Novo Nordisk Dependent On GLP-1s, Even Perceived Price Pressures Can Hurt " - Scrip, 9 Aug, 2018.)*

POTENTIAL COMPETITORS

Lilly leads a group of companies evaluating the role of candidate molecules displaying glucose-dependent insulinotropic polypeptide (GIP) agonism in metabolic diseases, alone or combined with GLP-1 and glucagon receptor agonist activity, according to the drugs development database, Biomedtracker.

Potential competitors include Novo Nordisk with NN9423, a triple GLP-1, glucagon and GIP receptor agonist, and **Sanofi** with SAR438335, a dual GLP-1 and GIP receptor agonist, both of which are in Phase I studies, Biomedtracker notes. Other companies with Phase I incretin modulating drugs include Denmark's **Antag Therapeutics ApS** with an unnamed GIP antagonist program, and South Korea's **Hanmi Pharmaceutical Co. Ltd.**. with HM15211, a triple GLP-1, glucagon and GIP receptor agonist, which is in Phase I studies for obesity and NASDH.

Further back in development is San Francisco, CA-based **Carmot Therapeutics Inc.**, with GLP-1 selective agonists and GLP-1/GIP dual agonists in preclinical studies for type 2 diabetes, and Denmark's **Zealand Pharma AS** with ZP-I-98, a long-acting GIP receptor agonist in preclinical studies and a GLP-1/glucagon agonist in Phase I for obesity and type 2 diabetes, partnered with Boehringer Ingelheim.

LY3298176'S RESULTS

In the Phase IIb 300-patient study, the effects of weekly doses of LY3298176 in 1 mg, 5 mg, 10 mg and 15 mg doses were compared to the effects of placebo and dulaglutide (Lilly's marketed once-weekly GLP-1 agonist, *Trulicity*) 1.5 mg in type 2 diabetics. The investigational compound improved blood sugar levels in a significant and dose-dependent manner, with mean absolute HbA1c level reductions from baseline being -1.6%, -2%, and

-2.4% with 5 mg, 10 mg and 15 mg doses of LY3298176, -1 .1% with dulaglutide and 0.1% with placebo.

Patients treated with LY3298176 lost significant amounts of weight compared with placebo, ranging from a mean of 4.8 kg on the 5 mg dose to a mean 11.3 kg on the 15 mg dose. Dulaglutide 1.5mg was associated with a mean weight loss of 2.7 kg, while placebo treated patients gained a mean 0.4 kg of weight. The most common side effects of LY3298176 included nausea, diarrhea and vomiting, which occurred mainly during a dose titration period, and were similar to side effects seen with GLP-1 agonists.

FULL EASE RESULTS

Lilly and Boehringer Ingelheim announced at the EASD meeting on Oct. 4 that empagliflozin met the primary efficacy endpoint, defined as a change from baseline in HbA1c versus placebo after 26 weeks of treatment, for all doses investigated (2.5 mg, 10 mg and 25 mg) in the Empagliflozin as Adjunctive to inSulin thErapy (EASE) Phase III program in adults with type 1 diabetes. The EASE program results were also published online in the journal, *Diabetes Care*.

The EASE-2 study evaluated doses of 10 mg and 25 mg of empagliflozin as an adjunct to insulin over 52 weeks, while the EASE-3 study evaluated doses of 2.5 mg, 10 mg, and 25 mg of empagliflozin as an adjunct to insulin over 26 weeks.

In EASE-2, placebo-corrected mean change from baseline in HbA1c at week 26 was -0.54% and -0.53% for empagliflozin 10 and 25 mg, respectively, while in EASE-3, placebo-corrected mean change from baseline in HbA1c at week 26 was -0.28%, -0.45% and -0.52% for empagliflozin 2.5 mg, 10 mg and 25 mg, respectively. In addition to reductions in HbA1c, empagliflozin achieved secondary endpoints including reductions in weight, decreases in blood pressure, and decreases in total daily insulin dose. There was a reduction in patient-reported hypoglycemic events, and the safety profile of empagliflozin was consistent with that previously reported in type 2 diabetics, the company said. *Published online 4 October 2018*

Roche's Hemlibra Wins Expanded FDA Approval, Opening The Door To Broad Hemophilia A Opportunity

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An expanded indication for **Roche**'s *Hemlibra* (emicizumab-kxwh) to prevent or reduce bleeding episodes in adults and children with hemophilia A without factor VIII inhibitors will significantly increase the commercial opportunity for the drug. The Swiss drug maker announced the FDA approval of Hemlibra for routine prophylaxis in the expanded population Oct. 4.

Hemlibra was originally approved in the US for hemophilia A in patients with factor VIII inhibitors in November 2017, but the initial approval was for a small subset of the market. Inhibitors are antibodies that develop when the immune system views infused clotting factor as a foreign substance to be attacked, before it has time to stop the bleeding. Inhibitors are more common in severe hemophilia, but only occur in about 5%-7% of all people with hemophilia A. About 20,000 people in the US have hemophilia, the majority of which have hemophilia A, according to Roche.

Now, Hemlibra will be the only prophylactic treatment for all people with hemophilia A, with and without inhibitors. It is also dosed subcutaneously and administered at different dosing options (once weekly, every two weeks or every four weeks). Other treatment options for people with hemophilia A require intravenous infusions more than once per week.

Hemlibra - originated and licensed to Roche by the Swiss company's Japanese affiliate **Chugai Pharmaceutical Co. Ltd.** - is poised to be a competitive force in the hemophilia market, given strong efficacy and convenient administration. It works differently from current factor VIII replacement therapies as a bispecific factor IXa- and factor X-directed antibody. The two factor proteins are required to activate the natural coagulation cascade and restore the blood-clotting process for patients.

Roche priced the drug at launch at a 50% discount to the only other treatment approved for patients with inhibitors, **Shire PLC**'s *Feiba* (anti-inhibitor coagulation complex), at a wholesale acquisition cost of $492,000 a year after the first year, which includes an extra loading dose (with prices based on the average patient weight).

Feiba has been the standard of care for hemophilia A patients with inhibitors. However, the expanded approval of Hemlibra is expected to impact more rival factor replacement therapies, including **Sanofi**'s *Eloctate*, acquired earlier this year with **Bioverativ Inc.**, Shire's *Advate* and *Adynovate,* and **Bayer AG**'s *Kogenate*, Kovaltry and the newly launched long-acting *Jivi*.

Roche said the annual WAC of Hemlibra for an average weight person with hemophilia A is less than the annual WAC of the two most commonly used prophylactic treatments for people without factor VIII inhibitors, Eloctate and Advate.

The FDA approval is based on two Phase III studies, HAVEN 3 and HAVEN 4. In HAVEN 3, adults and adolescents age 12 and older with hemophilia A without factor VIII inhibitors who received Hemlibra once weekly or every two weeks experienced a 96% and 97% reduction, respectively, in treated bleeds, compared to those who received no prophylaxis. The single-arm HAVEN 4 trial tested Hemlibra prophylaxis every four weeks in adults and adolescents 12 and older with factor VIII inhibitors and without, demonstrating clinically meaningful bleeding control.

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Acacia Aghast As FDA Says No To Barhemsys

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Acacia Pharma Ltd. says it is business as usual despite being left gobsmacked by a rejection from the FDA for its post-operative nausea and vomiting (PONV) therapy *Barhemsys* (low-dose amisulpride injection) due to concerns about a facility of its contract drug manufacturer.

The UK firm, which listed on the Euronext stock exchange in Brussels in March this year, has been hit with a complete response letter which identified deficiencies that had been reported during a recent pre-approval FDA inspection of a facility of the unidentified contract manufacturer of amisulpride that Acacia uses. On a conference call, CEO Julian Gilbert said that the company was very surprised to get the news but stressed that it was encouraged that the US agency "has not identified any problems with the extensive clinical and non-clinical data package submitted on Barhemsys, nor with the quality of the finished product."

The fact that the FDA has not found any inadequacies regarding the purity or stability of the active ingredient, or indeed the manufacturing process, is particularly galling for Acacia. When asked by *Scrip* about the identity of the contract manufacturer, Gilbert limited himself to saying that it supplies amisulpride (a dopamine receptor antagonist which is already marketed for schizophrenia) in Europe and the US.

When questioned as to whether Acacia would consider getting another supplier, he noted that the firm has worked with other firms and that could be an option "but that is not our preferred route." Gilbert said he believed the issue can be "expeditiously resolved" and the company intends to seek "urgent clarification from FDA and the contract manufacturer as to the status and procedure for resolution of the deficiencies that have been identified."

When pressed as to when Acacia knew about the potential problem, he said the company had been informed of correspondence between the FDA and the supplier before getting the CRL but getting the rejection letter was very much a surprise.

The CRL for Barhemsys, formerly known as Baremsis, which was submitted to the FDA on the back of data from four positive Phase III studies in more than 3,300 surgical patients and healthy volunteers, is undoubtedly a setback, and Acacia's share price has taken a pummeling. However, Gilbert stressed that the company is continuing to prepare for an anticipated launch of Barhemsys in the first half of 2019.

The FDA has not found any inadequacies regarding the purity or stability of the active ingredient, or indeed the manufacturing process

Acacia has been working on recruiting a US sales force of around 60-100 reps, which will focus on anesthetists at around 1,600 US hospitals that account for about 80% of relevant surgical procedures. The PONV market is a potentially very lucrative one, and the company estimates that approximately 65 million surgical procedures are conducted in the US each year that require injectable analgesia and are eligible for antiemetic use to prevent PONV – currently the options for PONV include 5HT3 antagonists such as ondansetron or corticosteroids like dexamethasone, which have limitations.

Acacia, which was founded in 2007 and is based in Cambridge, with US operations run out of Indianapolis, estimates that the total market in the US for prophylactic and rescue treatment (its New Drug Application to the FDA covers both) comprises 34 million treatment events annually and notes that PONV is regularly ranked as the most undesirable of all surgical complications by patients. PONV can also delay hospital discharge and result in re-admission, so if Barhemsys can cut hospitalization time – and the considerable associated costs – Acacia could have a promising product on its hands.

After the CRL, however, it will now have to refile the drug with the FDA. The company did not specify the financial impact that the delay will have but on the conference call, chief financial officer Christine Soden noted that Acacia had around £35m in cash and equivalents at the end of June and had already informed investors that further funds will be required in the near term for successful commercialization of Barhemsys in the US; the plan in Europe is to find a partner.

The company is also developing APD403, again repurposed amisulpride but in both intravenous and oral forms, for chemotherapy-induced nausea and vomiting (CINV). A Phase II study is scheduled to start in 2019.

Published online 8 October 2018

Boston Bags Assets From GSK and Novartis

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Boston Pharmaceuticals Inc. is the latest beneficiary of big pharma companies paring down their R&D portfolios, after getting hold of early-stage assets from **GlaxoSmithKline PLC** and **Novartis AG**.

First up, Boston has in-licensed five programs from GSK, which include two Phase II-ready candidates. GSK3352589 is a novel small-molecule inhibitor of rearranged during transfection tyrosine kinase which will be developed for irritable bowel syndrome with diarrhea, while GSK3008356, a small-molecule inhibitor of diglyceride acyltransferase (DGAT) 1 is being evaluated as a treatment for acne.

As for the other three candidates, GSK3183475 is a bromodomain inhibitor which has potential as a topical formulation to treat vitiligo and/or psoriasis and is Phase II-ready. The pact, for which financial details have not been revealed, also includes two undisclosed preclinical programs that already have specific lead candidates.

Boston has also acquired worldwide rights to three novel anti-infectives from Novartis comprising two complementary candidates targeting carbapenem-resistant *Enterobacteriaceae* and an oral, first-in-class LpxC inhibitor for *Pseudomonas* infections. The Swiss major will receive an upfront payment and is entitled to royalties and milestone payments and has also taken an equity stake in two new companies formed together with Boston to further develop and commercialize these programs.

Jay Bradner, president of the Novartis Institutes for BioMedical Research, said in a statement that "the need for new antibiotics that address drug-resistant bacteria is clear and we are pleased to find a partner in Boston who will dedicate the appropriate expertise and resources for the further development and commercialization of these programs."

The deal comes less than three months after Novartis declared that it was pulling the firm's antibacterial and antiviral research programs to prioritize resources in other areas. The Basel-based group has been narrowing its R&D focus since Vas Narasimhan took over as CEO in February this year, concentrating on oncology and rare diseases and exploring cell and gene therapy approaches.

GSK has also been clearing out assets since July last year when CEO Emma Walmsley announced that the company would terminate, partner or divest more than 30 preclinical and clinical programs. In July, the UK giant inked a $330m deal with **Dermavant Sciences Ltd.** to sell the Phase III-ready tapinarof, with $150m of that coming in an upfront payment. *(Also see "Walmsley Shakes Up GSK; Cuts More Than 30 Drug Development Programs" - Scrip, 26 Jul, 2017.)(Also see "Roivant Splashes Cash Again To License GSK Skin Disorder Drug" - Scrip, 13 Jul, 2018.)*

UP-FOR-SALE ALBIGLUTIDE IMPRESSES IN TRIAL

Another drug that GSK is looking to divest is albiglutide, the diabetes drug which has been taken off the market in the US and Europe where it was sold as *Tanzeum* and *Eperzan* respectively. The company presented positive data from the Harmony Outcomes study of the GLP-1 receptor agonist at the European Association for the Study of Diabetes congress in Berlin on Oct. 2, which showed that albiglutide, administered subcutaneously once-weekly in 9,463 patients over a median period of 1.6 years was superior to placebo in reducing the risk of major adverse cardiovascular events by 22% when used in addition to standard of care in patients with type 2 diabetes and cardiovascular disease.

The study was initiated in July 2015 and despite Walmsley's announcement in July 2017 of the firm's intention to cease further activities for albiglutide, John Lepore, senior vice president for GSK's R&D pipeline, said that Harmony Outcomes was "an important study for us to complete to generate new data and insights about the role of the GLP-1 receptor agonist class in the management of patients with diabetes and CV disease."

Tanzeum and Eperzan struggled to make any inroads into the market share held by GLP-1 blockbusters such as **Novo Nordisk AS**'s *Victoza* (liraglutide) and **Eli Lilly & Co.**'s *Trulicity* (dulaglutide). Lepore added that "we continue to explore opportunities to divest this medicine to a company with the right expertise and resources to realize its full potential."

As for Boston, which is backed by Gurnet Point Capital, the healthcare fund founded by Swiss entrepreneur Ernesto Bertarelli and led by former **Sanofi** CEO Chris Viehbacher, the GSK and Novartis deals will virtually double its pipeline. Other compounds in there include BOS-161721, which targets interleukin-21 and is currently in Phase I for lupus and was licensed from **AstraZeneca PLC**, as well as a RET (ret proto-oncogene) kinase inhibitor licensed from **Daiichi Sankyo Co. Ltd.**, which is also in Phase I for non-small cell lung and medullary thyroid cancers.

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J&J Bets Big On Arrowhead's Early Promise In Hepatitis B

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Johnson & Johnson saw the promising interim data **Arrowhead Pharmaceuticals Inc.** unveiled at a conference in New Zealand a month ago for ARO-HBV, its gene-silencing candidate for hepatitis B, and decided to license the candidate, invest in Arrowhead and collaborate with the biotech on up to three additional novel targets in a deal announced Oct. 4.

J&J is one of several companies working toward a combination therapy regimen that might yield a functional cure for HBV – it already has five clinical candidates for HBV in development, according to Biomedtracker.

While J&J's **Janssen Pharmaceuticals Inc.** unit is placing a major bet on Arrowhead's RNA-interference technology and the subcutaneous delivery platform Arrowhead pivoted to only two years ago, the deal also will enable the Pasadena, Calif., firm to wager big on some of its other projects. During a same-day investor call, Arrowhead CEO Christopher Anzalone said the firm now will focus on other programs centered around "validated targets, understandable regulatory pathways and clear commercial opportunities."

These include Phase I ARO-AAT for liver disease associated with alpha-1 antitrypsin (AAT) deficiency and a pair of lipid-lowering preclinical candidates Arrowhead hopes to advance toward the clinic before the end of 2018: ARO-APO3 for hypertriglyceridemia and APO-ANG3 for dyslipidemia. Anzalone noted that Arrowhead will detail these and other pipeline efforts more fully during an R&D day slated for Oct. 16 in New York.

The deal brings Arrowhead $175m in upfront cash, plus a $75m equity investment by **Johnson & Johnson Innovation - JJDC Inc.**, priced at $23 per share. Arrowhead's stock finished the Oct. 4 trading down 17.4% to $15.33 per share. The biotech will complete an ongoing Phase I/II study of ARO-HBV, with Janssen taking over for Phase IIb and responsible for all development and commercialization costs at that point.

In an interim look at the Phase I/II study presented at the World Gastroenterologists Summit in Auckland Sept. 6, Arrowhead reported a 99% mean reduction in HBV surface antigen (HBsAg) at day 85 in a group receiving a 100 mg dose of ARO-HBV and a 96% mean reduction in HBsAg at day 71 in a 200 mg dose cohort. The five-cohort, ascending-dose study also is testing 300 mg and 400 mg doses of the candidate, with a placebo arm.

In a Sept. 6 note, LifeSci Capital analyst Patrick Dolezal pointed out that one patient experienced a 99.99% clearance of HBsAg, "which is the most dramatic HBsAg reduction we've seen to date so soon into treatment, and likely means that this patient has a good shot at eventual seroclearance." Current HBV therapy treats the virus as a chronic, lifetime condition because of the virus' ability to self-replicate.

Arrowhead can earn a $50m development milestone when Janssen initiates a Phase II trial, expected during 2019, and then up to $1.6bn in milestones plus sales royalties if ARO-HBV reaches market. The deal also includes a collaboration under which Arrowhead will discover and undertake preclinical work on candidates against three targets selected by Janssen that are not among those already being addressed by Arrowhead's pipeline. The biotech can earn up to $1.9bn in licensing fees and milestones, as well as potential royalties, in relation to this collaboration.

All told, including the expected $25m-$30m in clinical development costs Arrowhead now expects to save in 2019 by handing the HBV program over to Janssen, the deal means a near-term infusion about $325m toward the company's bottom line, Anzalone said, to go along with the roughly $90m it has in cash at present. The company also can earn up to $600m in milestones under an ongoing collaboration with **Amgen Inc.**, he added.

ADVANCING TOWARD FUNCTIONAL CURE REQUIRES MAJOR RESOURCES

Anzalone said J&J's expertise plus its deep pockets make it the ideal company to take ARO-HBV forward in an expensive indication, whose cost and complexity is only increased by the myriad directions in which investigating combination therapy could go.

Consensus has emerged that functional cure of HBV likely will require antiviral and immunomodulatory components and that reducing HBsAg to undetectable levels will be crucial.

"Why then should we enter into this partnership now?," Anzalone asked on the call. "Why not continue the leadership position we have created for ourselves and push deeper in the clinic toward the market? Sometimes leadership is about knowing where you can leave and when you should be part of a team. For this disease at this time in Arrowhead development, Janssen is simply better positioned to continue our forward progress and push ARO-HBV to market."

In a same-day note, William Blair & Co. analyst Katherine Xu said she was surprised Arrowhead out-licensed ARO-HBV so early, opining that the deal terms "do not appear to us as the most favorable at the present moment." Still, Xu maintained her "outperform" rating for Arrowhead's stock and upgraded her modeling of ARO-HBV, increasing the program's probability of success from 40% to 50% with

the Janssen deal and raising the candidate's peak earnings potential from $2.5bn to $3.4bn.

Anzalone said Phase IIb studies of ARO-HBV will be "large, expensive and complicated." Based on the biopharmaceutical industry's experience in developing curative combination therapies for hepatitis C, a large pharma like J&J is best suited to take on this commitment, he asserted.

"The industry's experience with hepatitis C is telling us speed, experience in large complex clinical studies and established commercial infrastructure will be critical for success," the exec said. "Janssen has these capabilities, while Arrowhead is not yet tooled for this, at least not yet and not for this disease. So, it clearly makes sense to partner ARO-HBV with Janssen at this time from a strategic standpoint, and economics, both guaranteed and contingent, make this deal transformational for us."

The deal with J&J demonstrates rapid success for Arrowhead after it abandoned in November 2016 its entire clinical pipeline – including a pair of HBV candidates that had shown promising efficacy – due to safety issues. Its most advanced HBV candidate, ARC-520, was stalled when the US FDA placed the Phase IIb Heparc-2004 study on clinical hold due to deaths seen in high-dose non-human primate toxicology studies using Arrowhead's EX1 intravenous liver-targeted delivery technology.

Within three weeks, Arrowhead shuttered all programs using the EX1 delivery mechanism and began a process of moving candidates using its next-generation subcutaneous delivery system into clinical development, more or less starting over as a clinical-stage biotech. Arrowhead cut staff by 30% on this decision and sustained a 67.2% decline in its share price on the day the overhaul was announced.

"We went from a standing start to the current clinical evidence of activity involving more than 100 human subjects across both programs [ARO-HBV and ARO-AAT] in well less than two years," Anzalone told the call. Now, with the Janssen deal and its remaining clinical and preclinical pipeline, Arrowhead has "good technology, good drug candidates, a strong balance sheet and access to growth capital," he added.

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GSK-Backed Sitryx Launches With Six Immunometabolism Eggs In Its Basket

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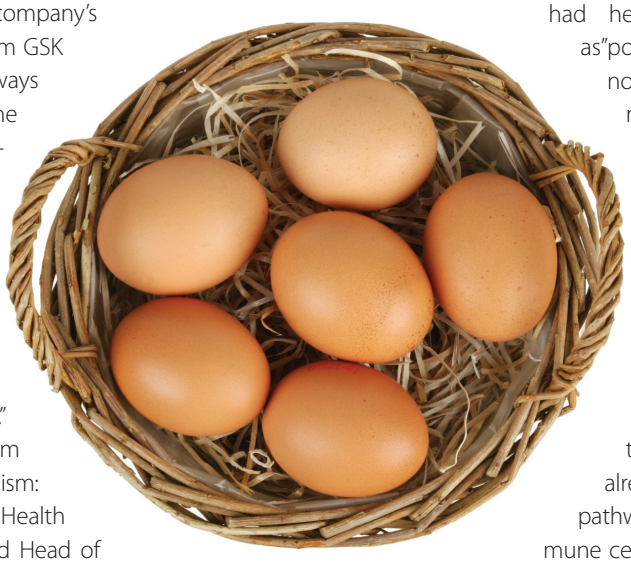
Chemical assets from **GlaxoSmithKline PLC** and target biology insights from high-profile academic founders form the basis for new company **Sitryx**, which has been launched with $30m in series A funding. Focused on developing disease-modifying treatments for autoimmune/inflammatory conditions and cancer, it is working on six early-stage projects to target immunometabolic pathways with small-molecule candidates. The company sprang out of the Immunology Network set up at GSK by Paul Peter Tak, who last month left the company after seven years and who is a co-founder of Sitryx.

"We have set ourselves up to be leaders in the field of immunometabolism," explained CEO Neil Weir, who joined the company as its first employee in April 2018. He was previously SVP Discovery at **UCB Pharma**. The company's assets include the tangible assets from GSK and "biological insights into pathways and as yet unpublished data from the founders' labs around the connectivity of targets to human disease," Weir told *Scrip*. "We've not encamped in one specific area; our targets cover a broad range of metabolic pathways through the insights that have come from our founders in glycolysis, the TCA [tricarboxylic acid] cycle and in pathways that feed into the TCA cycle."



Sitryx has six academic founders from the world of immunology and metabolism:

- Houman Ashrafian – Partner at SV Health Investors and Visiting Professor and Head of Experimental Therapeutics at University of Oxford
- Luke O'Neill – Professor of Biochemistry, School of Biochemistry and Immunology at Trinity College Dublin
- Jonathan Powell – Professor of Oncology and Associate Director, Institute for Cancer Immunotherapy, Johns Hopkins University
- Jeff Rathmell – Professor of Cancer Biology and Director, Vanderbilt Center for Immunobiology
- Michael Rosenblum – Assistant Professor, UCSF School of Medicine
- Paul Peter Tak – formerly Chief Immunology Officer and SVP at GlaxoSmithKline, and Professor of Medicine at Amsterdam University Medical Centre

Tak explained to *Scrip* that it had been Luke O'Neill through his work with GSK's Immunology Network who had helped identify immunometabolism as "potentially the next big thing in immunology." Unlike previous work targeting metabolic pathways to starve tumor cells, "this is a fundamentally different approach where you actually target metabolic pathways to interfere with the immune system and thereby target the tumor cell," Tak said, noting that such an approach is also relevant to diseases of auto-immunity.

While the fundamentals of metabolism are a fairly well understood already, attempting to drug metabolic pathways to change the behavior of immune cells is still an emerging field, explained Weir. "And from what we can see and with the way

we're pursuing our targets, we're not seeing other competitors." With the breadth of experience of the founders and knowledge around different targets, Sitryx "doesn't have all our eggs in one basket," added the CEO: "There's a breadth of portfolio here, it's not just a single project. And it covers both innate and adaptive immune responses."

The company is still at an early stage, and does not expect to begin identifying candidates to take into the clinic until late 2019, with first in human trials not expected before 2020.

To date, immuno-oncology has focused in large part on stimulating cell surface receptors using antibody treatments, but Sitryx is looking to develop small molecule oral and topical therapies that influence processes inside the cells. There may be potential to develop such treatments to be complementary to other therapies, but the company's starting point is to view its candidates as standalone therapies, Weir said.

The programs are split between autoimmune/inflammatory and oncology conditions but "we will follow where the biology takes us, having set out on a path which starts off with a hypothesis as to where it's pertinent," the CEO noted, adding that the approach could also be applied to fibrosis.

Sitryx will have its own labs in Oxford Science Park but it will also work with founders, placing post-docs in their labs, as well as working with CROs. And GSK will support the company, for example helping it to understand and apply PROTACS (proteolysis targeting chimera) technology.

The series A round was co-led by SV Health Investors and Sofinnova Partners, with GSK and Longwood Fund also investing. GSK has no special rights on candidates emerging from Sitryx's pipeline.

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Aduro Says End Of Janssen Collaborations 'Not A Lethal Blow'

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Aduro BioTech Inc. quietly revealed in an Oct. 1 SEC filing that a pair of partnerships signed with **Janssen Biotech Inc.** in 2014 have ended, but management maintains the **Johnson & Johnson** affiliate's decision was expected and not a lethal blow of any kind for its prospects going forward.

In an 8-K filing, Aduro reported that Janssen informed it on Sept. 25 that it was terminating a pair of partnerships using the biotech's proprietary attenuated strains of *Listeria* bacteria to present tumor-associated antigens to treat prostate and lung cancer. Janssen will return the ADU-214, ADU-741 and GVAX Prostate vaccine candidates and related intellectual property by Dec. 24, but Aduro has no plan to continue the programs on its own, CEO Stephen Isaacs told *Scrip*.

All of those [collaborations] will effectively end and we will have no formal relationship with Janssen at that point," he said. "But I will say that the relationships with the [Janssen] scientists and the management remain very strong. We've been collaborating with them on scientific matters for a long time. … They're a great group to work with, there's a lot of mutual respect between our organizations – it's just that for these particular projects, the biology didn't work out, and that happens."

Aduro's stock price seemed to level out Oct. 3, after failing the first two days of the week. The stock declined 2.4%, closing at $7.18 per share on Oct. 1, the day of the SEC filing, then tumbled 13% to close at $6.24 per share on Oct. 2. On Oct. 3, Aduro shares ended the trading down 1.4% to $6.16 apiece.

> 'They just were not getting the clinical results that they'd hoped for in light of other options.'

After licensing the programs to Janssen in 2014, Aduro began moving its live attenuated double-deleted (LADD) Listeria platform into other indications, including mesothelioma and gastric and ovarian cancer, Isaacs said. Janssen took over the prostate and lung cancer efforts, and eventually slowed the pace on the prostate cancer program while awaiting lung cancer data, which proved to be disappointing for Janssen, he acknowledged.

"They just were not getting the clinical results that they'd hoped for in light of other options," Isaacs explained. "It just wasn't getting them where they wanted to go, so they decided to stop."

Aduro earned about $42m in upfront cash under the two deals and also realized milestones that increased its aggregate take from the partnerships to about $100m, the exec estimated. Seeing how the LADD programs were performing – both internally and at Janssen – Aduro removed additional earnouts from the deals from its modeling about two years ago, he added.

"The fact that they're going away really has no impact on our ability [to continue]," Isaacs said. "We have $300m in the bank and no debt. So, it's not consequential to us; it's unfortunate, biology is complicated, but it's not a lethal blow or anything to us."

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Scrip Awards Finalists 2018

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Best Company in an Emerging Market

Scrip's Best Company in an Emerging Market Award seeks to reward the growing pharmaceutical industry founded in areas beyond its traditional geographic borders of North America, Western Europe and Japan.

Beximco Pharmaceuticals

Beximco Pharma continues to build its presence in emerging and developed markets. It launched nine new products in its domestic market and began exporting to Canada, Uzbekistan and Zambia. It also acquired a majority stake in Nuvista Pharma, a leading Bangladeshi pharma company specialising in hormones and steroid drugs.

Biocon

Biocon established its credibility as a global biologics player by successfully navigating the complexities in the research, development, manufacturing and regulatory approvals of these advanced therapies. It was the first company to get a biosimilar trastuzumab approved in the US and was among the first to receive insulin glargine approval in Europe.

CinnaGen Pharmaceutical Group

CinnaGen plays a leading role in improving healthcare systems, not only in its home country of Iran but also in the MENA region. The group has launched 13 biosimilar medicines, using cutting-edge technology, into the Iran market. Over half a million patients used CinnaGen medicines last year, a growth of 18%.

Hutchison China MediTech (Chi-Med)

Chi-Med has emerged as a leading, fully-integrated, China-based healthcare group, positioned as a risk-balanced globally focused biopharma company, active in researching, developing, manufacturing and commercializing pharmaceuticals and health-related consumer products such as fruquintinib. In late 2017, Chi-Med also completed a Nasdaq follow-on offering, raising net proceeds of $292.7m.

Mundipharma Singapore

With its regional emerging markets hub in Singapore – and a global network across the Asia-Pacific, Latin America, the Middle East and Africa – Mundipharma's medicines now reach patients in 128 countries in six continents. In tandem with its patient-centric approach, Mundipharma's entrepreneurial spirit has enabled the company to grow its portfolio to over 38 medicines.

WuXi Biologics

Working with the proceeds of its June 2017 IPO, and a 230% stock price market growth achieved since, China's WuXi Biologics has started constructing three new drug development and manufacturing sites, including one in Ireland. It also passed a significant milestone by being approved by the US FDA to manufacture a commercial biologic drug.

Community Partnership of the Year Award (Sponsored by Medidata)

This Scrip Award is designed to acknowledge the numerous ways in which pharma and biotech companies give back to the wider community.

AstraZeneca's Mentoring Team

AstraZeneca has expanded its business mentoring initiatives in Cambridge: to support Accelerate@Babraham, a new bio-incubator and life science accelerator at the Babraham Research Campus; a collaboration with Lucy Cavendish College to support advancing women in science and business leadership; plus it has launched its AstraZeneca Start-Up Science competition to support life sciences start-ups.

Beximco Pharma with DSM Nutritional Products and Sight & Life Global Nutrition Research Institute to improve nutrition in rural Bangladesh

This tripartite effort aims to support, for free, community nutrition and health research intended to test, discover, inform and guide policies that can lift the health burden of micronutrient deficiencies from women, infants and children in impoverished regions of rural Bangladesh and South Asia.

IQVIA India's Race for 7 with the Organization for Rare Diseases India

For the first time since its inception, Race for 7 expanded beyond Bangalore to Mumbai and Washington. The event drew close to 6,000 participants across three cities, including rare disease patients, their caregivers, healthcare professionals and the general public, all united by a common cause – to commemorate World Rare Disease Day.

Oxford PharmaGenesis' Open Pharma

Open Pharma is a partnership of the pharmaceutical industry, publishers, patients, academics and regulators, which aims to identify and make the changes needed to improve transparency and accessibility of medical research. It has led to meaningful policy and behavioural changes, including the launch of the first pharmaceutical company open access policy.

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SWITCHING FOCUS TO STING, APRIL MECHANISMS

The Listeria platform was one of three major efforts Aduro had been working on and it now will focus almost entirely on the other two – a *STING* (Stimulator of Interferon Genes) agonist program in multiple tumor types that was partnered in with **Novartis AG** in 2015 in a deal that brought $250m up front and its *APRIL* (A Proliferation-Inducing Ligand) antibody program in multiple myeloma. It is also working on STING antagonist candidates for autoimmune indications and is developing a CTLA-4 inhibitor cancer immunotherapy in Europe that it sees as an out-licensing opportunity, Isaacs said.

All of those programs are wholly owned except the STING agonist work in collaboration with Novartis. There, the companies are investigated ADU-S100, a cyclic dinucleotide, in solid tumors, along with combination study with Novartis' investigation anti-PD-1 candidate spartalizumab and another combo study with an anti-CTLA-4 compound. Next year, an additional combination trial testing ADU-S100 with **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) will start, Isaacs noted.

"STING is a very hot field," he said, "the STING receptor is sort of the central mediator of innate immunity and we developed these specific cyclic dinucleotides, because we're very strong in organic chemistry, that bind to STING and turn on innate immunity that leads to an adaptive immune response."

In the partnership with Novartis, the studies are focusing on "any cancer that produces a dermally acceptable lesion that we can inject," Isaacs explained. These tumor types include melanoma, squamous cell and basal cell carcinoma, head-and-neck cancer, metastatic prostate cancer and some gastrointestinal cancers, he said.

While turning STING on may prove an effective way to fight cancer, Aduro also has learned that STING overstimulation can cause an autoimmune response. Therefore, separate from the Novartis tie-up, it is studying antagonists that may offer therapeutic potential in autoimmune disorders such as rheumatoid arthritis, lupus and several monogenic diseases, Isaacs said. Right now, that work is in lead optimization.

Aduro's anti-APRIL program is now in a dose-escalating Phase I trial in multiple myeloma and the company also plans to study the mechanism in IGA nephropathy. Separately, Aduro's work in the APRIL target yielded an anti-CD27 agonist that the company out-licensed to **Merck and Co**. The New Jersey pharma has that candidate in Phase I, Isaacs said.

Meanwhile, Aduro plans to complete its work in one ongoing Listeria project and then step away from that approach, he added. Mirroring the neoantigen work being done by companies like **Momenta Pharmaceuticals Inc.**, **Neon Therapeutics Inc.** and **BioNTech AG**, Isaacs said, Aduro decided to see what results a personalized LADD (pLADD) approach would bring. Early in 2017, it signed a collaboration with **Stanford University** to help to pick the antigens for this effort. All previous efforts with the Listeria platform focused on self-antigens that are overexpressed in certain types of cancer, he explained, asked whether neoantigens could induce a stronger immune response.

An ongoing Phase I study has yielded what Isaacs termed an "impressive immune response" in one patient, but the company only plans to finish dosing 13 other patients, compile the data and then end the program. It has been de-emphasizing its Listeria platform in favor of the STING and APRIL mechanisms for about 18 months now, the CEO noted.

"We'll look at that [data] in the aggregate," Isaacs said. "I think that could make a very strong licensing case and we'd be interested in doing that. We're also very active in China now, so there might be interest there. We'll go where the data take us and if we can make a licensing deal around it, we'll do it. It's just that we're not going to prioritize it internally anymore."

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Roche Registers Fresh Win For New Flu Drug

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Roche has presented a positive update on a late-stage trial of its closely watched influenza drug baloxavir marboxil a couple of months before the FDA is set to decide on approval for the first therapy in a new class for the virus in two decades.

The Phase III CAPSTONE-2 study showed that treatment with baloxavir, a single-dose, oral medicine that is the first in a new class called endonuclease inhibitors, significantly reduced the time to improvement of influenza symptoms versus placebo (median time of 73.2 hours versus 102.3 hours) in people at high risk of serious complications from the flu. The drug, which was developed by **Shionogi & Co. Ltd.** which sells it in Japan as *Xofluza*, was well-tolerated and no new safety signals were identified.

Baloxavir also demonstrated an improvement of symptoms overall compared with Roche's established influenza blockbuster, the neuraminidase inhibitor *Tamiflu* (oseltamivir), but Mark Eisner, the company's global head of respiratory and infectious diseases told *Scrip* that it was slight and not statistically significant (73.2 hours for baloxavir compared with 81.0 hours for Tamiflu). However, he was particularly enthused about data on a subpopulation of patients with influenza type B, where antivirals have shown only limited efficacy or inconclusive data; in this group, baloxavir was significantly more efficacious than Tamiflu in reducing the time to improvement of symptoms (74.6 hours versus 101.6 hours).

On the overall results, Eisner said that the 2,184-participant study was significant given that it included adults 65 years of age or older, who have conditions such as asthma, chronic lung disease, morbid obesity or heart disease, patients defined by the Centers for Disease Control and Prevention (CDC) in the US and other public health bodies as high risk. He added that CAPSTONE-2 is the first Phase III trial to demonstrate a significant and very clinically meaningful benefit in people at high-risk for complications from the flu for which there are no currently approved drugs. *(Also see "Scant Pipeline Competition For Roche's Novel Flu Antiviral" - Scrip, 26 Jun, 2018.)*

The FDA granted a priority review to baloxavir in the summer based on the CAP-

STONE-1 study and a Phase II study, setting an action date of December 24. Eisner said he understood the excitement around the drug, noting that if all goes well with the agency, the drug is "going to be the most potent antiviral on the market for influenza, offering the first new mechanism of action in 20 years." Timing on a submission in Europe is still being discussed internally, he added.

Commenting on the data, Karolina Kujawa, an analyst at Datamonitor Healthcare, told *Scrip* that "it is extremely important to conduct trials in people at higher risk of flu complications," noting that Tamiflu for example does not have data for immunocompromised patients, "so this could give baloxavir an additional advantage to attract a new patient population." Success for baloxavir will eventually cannibalize Tamiflu's leading position in the flu market, she said, but Roche should be able to charge a premium price given baloxavir's improved dosing schedule (Tamiflu treatment involves two pills a day for five days) and its potential to reduce transmission of the virus.

Kujawa noted that she was still waiting for detailed data from CAPSTONE-2, which will be presented as a late-breaking oral presentation during IDWeek 2018 in San Francisco on Saturday (Oct. 6), but claimed that the lack of statistically significant improvement over Tamiflu "will probably limit the premium price the drug will be able to achieve."

Kujawa's colleague at Datamonitor Healthcare, Michael Haydock, agreed, although he stated in a recent analyst note that "while baloxavir did not demonstrate superiority compared to oseltamivir, this is not expected to be a significant hindrance to its uptake given its greatly improved dosing schedule." In terms of cost in the US – in Japan, the drug sells for around $40 for the one-pill dose – he also believes Roche is likely to pursue revenue growth via premium pricing but "the company will face competition from generic versions of oseltamivir and must therefore show restraint when setting baloxavir's list price."

Roche's Eisner noted that the CAPSTONE-2 data came out a week after CDC figures revealed that in 2017, the US experienced its deadliest flu season in over a decade, with 80,000 people dying from the virus. "We, and other agencies need to get the word out that this is a severe problem," he added, saying "I understand that for a patient it is difficult to get out of bed and see a doctor, but you are going to get better quicker."

Eisner also pointed out that earlier this month, Roche inked an agreement with the US government's Biomedical Advanced Research and Development Authority (BARDA) whereby the latter will contribute $43m over five years to support a study of baloxavir in treating severely ill patients hospitalized with seasonal or pandemic influenza viruses.

BARDA will also provide $19m over 18 months to advance the development of Roche's thrombolytic *Activase* (alteplase) for a new indication to treat acute lung injuries called cast formation caused by inhaling sulfur mustard gas.

Published online 4 October 2018

For Artificial Intelligence To Save Lives And Money, 'It Must Be Trusted'

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Machine learning artificial intelligence is already revolutionizing healthcare provision and the pace will only increase. So governments and institutions need to raise their game and become more proactive to avoid serious dislocations within the sector and allow innovative companies to take advantage of the trend, speakers told a London conference this week.

The London-based Institute of Engineering and Technology held its second ever conference on artificial intelligence on Oct. 3, this time focusing on AI's potential impact in the healthcare sector. Some speakers posed the question: can AI be trusted to make life-and-death decisions when it comes to healthcare?

The rapid development of AI in the healthcare sector is well-reported: the amount of data being accumulated by the life sciences industry and healthcare system is exploding as records such as medical histories are being digitized and stored on servers. Since machine learning requires vast amounts of data to improve, AI will gain from the data accumulation and continue to play an increasingly significant role in everything from diagnostics to pharmacology and beyond.

TRUST IN AI

But if the rules of the game are not made stringent enough, the public at large could reject the idea, impeding the transition which experts say is essential to allow R&D to become more efficient. This would slow the evolution of new methods of healthcare delivery and better informed clinical decision-making, and reduce the ability of patients to become more informed in managing their health.

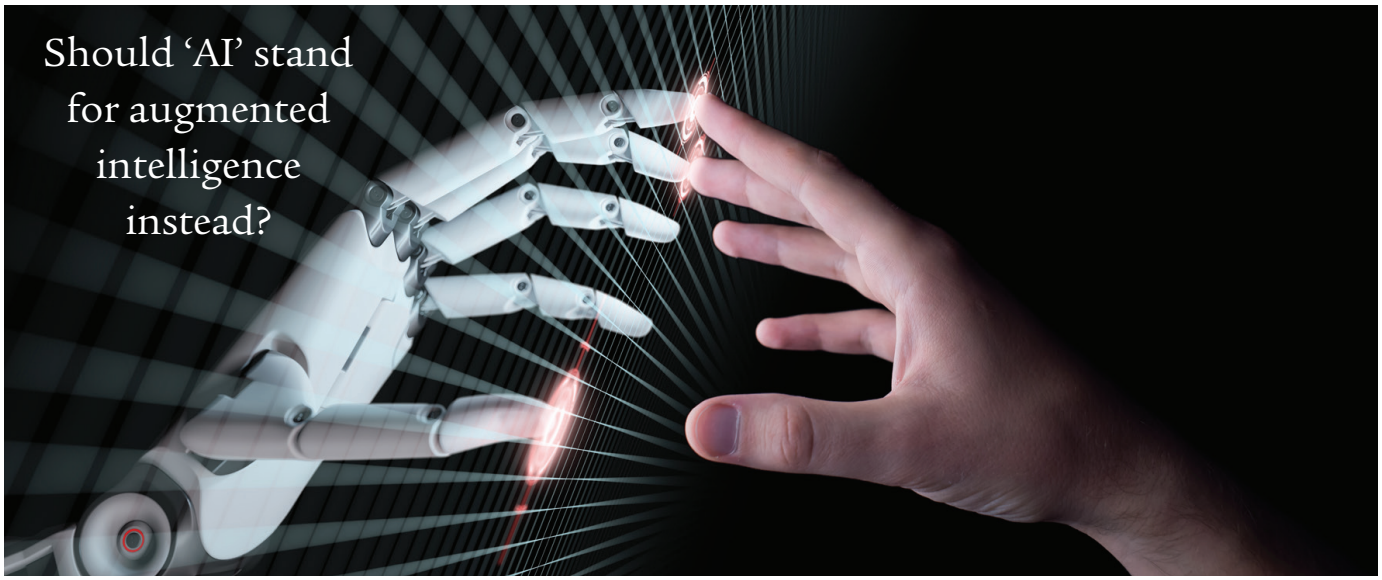
"We've got a perfect storm within healthcare provision, coupled with massive amounts of data available for building deep learning neural-networks and rapidly improving technology coming together at the same time. That's why every AI study you see has healthcare at the top of the list in terms of where AI and industry can have a real beneficial impact for society on a mass scale," said Peter Durlach, a healthcare strategist at Nuance Communications told the conference.

But Lord Clement-Jones told the same audience that building and sustaining public trust in AI was essential. Clement-Jones heads the the select committee on artificial intelligence appointed by the House of Lords in June 2017 whose task is to consider the economic, ethical and social implications of advances in artificial intelligence. In early 2018, the committee published it's 2017-2018 report, recommendations from which the government is seemingly embracing.

He told the conference: "I am a firm believer in the potential of AI in healthcare."

AI MUST NOT GO LIKE GMO

He noted examples of innovative science – such as genetically modified foods - where loss of trust has led to negative public



opinion towards the products. "We on the committee did not want that to happen with AI, given all its potential," Clement-Jones said.

He noted the influential role that the general media will have this process could be significant. "The learning capacity of AI and the resulting autonomy that it gives it is what we think distinguishes AI from previous technologies. But the terminator robot narrative is all too prevalent when people are talking about AI in our tabloids," he noted.

Regulation of AI must therefore be developed urgently and with adequate emphasis on ethics of use. "AI is here and now and one of the things we put in our report noted the fact that AI is already in our everyday lives. So AI is something that ethically, and legally and in regulatory terms we need to think about in the here and now," Clement-Jones said.

NHS NOT AI READY

Unfortunately for the UK, its National Health Service, or NHS, is extremely ill-equipped to adapt to the "brave new world" of AI, according to Clement-Jones.

"In our select committee report we said AI offered significant opportunities for the healthcare sector and there were some obvious areas such as scans and x-ray images and clinical and administrative aspects AI and healthcare – but we also considered whether the NHS was well positioned to take advantage of AI and we were rather concerned by the NHS's lack of organizational preparedness to embrace new technologies and the absence of a credible strategy to encourage the uptake in innovation and technology and scale it across the NHS. The digital revolution has largely by-passed the NHS," Clement-Jones said.

Adrian Weller, AI program director at the Alan Turing Institute spoke on behalf of many in attendance by saying "we want to encourage investment in AI - but we need AI that we can trust ... we don't want to trust technology too much because we don't want to be taken advantage of."

"That said, we need to move from principles to practice more quickly," Weller concluded.

AI CAN MEAN AUGMENTED INTELLIGENCE TOO

Peter Bannister, chairman of the Institution of Engineering and Technology's Healthcare Sector, moderated the conference and summed up its messages to *Scrip*: "The conference brought together people active in the ethical, legal, regulatory and business sides of AI. One takeaway is that is that self-regulation within the healthcare sector might be necessary rather than waiting for the laws to catch up."

He added: "The conference also discussed the difficult situation that we face socially, legally and ethically in order for the technology to realize its full potential. And the message at the end seemed to be that those actively engaged in AI are highly motivated to put together increasingly clear sets of guidelines, codes of practices or regulations to make it more straight forward for manufacturers who see an opportunity to bring machine-learning AI into the Healthcare space to solve some of today's big problems with regards to resourcing and bandwidth – while not making too many wrong turns regarding data ownership and ethics, and ultimately the liability around the relationship between the clinician and this technology."

The term "augmented intelligence" was suggested by one speaker as being a more appropriate label for the current stage of AI than artificial intelligence. Bannister thought that resonated with many at the conference.

"At least for the next few years, it will still be the clinician who's in charge of the decision making. The opportunity is that machine learning can help them manage the vast amounts of data they are being bombarded with year on year and which is increasing where, in principle, there's all this information available but they haven't a chance of trawling through all of that data and finding all the clinically actionable information. So augmented intelligence would definitely be welcomed by them," he said.

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VelosBio CEO: Series A Success Shows Investors Back His ADC Formula

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Developing and getting approved an antibody drug conjugate against cancer boils down to getting the right ADC formula comprising a targeted tumor, linker and payload, and VelosBio's CEO David Johnson says he and his team believe they have identified those components and that investors showed similar belief by backing the Seattle-based biotech's recent $58m Series A funding round.

VelosBio Inc. describes itself as a next generation oncology company which is developing antibody drug conjugates to target solid tumors and hematological cancers.

Its Series A funding round announced Oct. 1 was supported by new investors **Arix BioScience**, **Sofinnova,Chiesi** and **Pappas**, plus existing investors **Takeda Ventures** and **Decheng**. The ADC developer was originally seeded by Takeda Ventures in December 2017.

VelosBio was founded by CEO Dave Johnson and CMO Langdon Miller, both fresh from **Acerta Pharma BV**, the developer of approved blood cancer therapy *Calquence* (acalabrutinib) which was acquired by **AstraZeneca PLC** in 2015.

"One of the greatest challenges with ADCs has been to find a target that's truly tumor specific and expressed at a high enough frequency to make a difference when you're targeting a cancer. That was something all our syndicate investors focused on," Johnson said in an interview with *Scrip*.

"They looked at our data and thought what we were doing was special because we were going after a target that was truly cancer specific and we had a targeting mechanism that was ideally suited – an antibody that was ideally suited to carry an ADC payload directly to a tumor cell."

He declined to identify the target at this time.

"We've committed to our investors that we would stay silent on a specific target until after we initiate a Phase I 'first-in-human', and we'll be doing that in a few weeks," Johnson said.

"We will be submitting our IND to the FDA in the coming weeks and starting our Phase I first-in-humans study shortly thereafter. The target that we are going after is something that is expressed in a meaningful way in a number of hematological malignancies as well as important solid tumors," he said, but declined to give further details.

VelosBio also has a pipeline of early-stage assets that it will develop.

"The Series A funding gives us the capital to aggressively develop our pipeline programs and that was important for the participating investors," the CEO said. "Our investors wanted to ensure that in parallel with us putting this first program into the clinic that we also had the funding to rapidly develop our follow-on programs and make them a clinical reality in the coming months," Johnson said, without giving details.

He noted that one of VelosBio's backers is Takeda Ventures. "They know the ADC space quite well," he said, noting that **Takeda Pharmaceutical Co. Ltd.** and partner **Seattle Genetics Inc.** have recently made headlines with the expanded approval of their antibody drug conjugate *Adcetris* (brentuximab vedotin) in first-line Hodgkin lymphoma (it was originally approved by the FDA in 2011) and just this week announcing new data in peripheral T-cell lymphoma. *(Also see "Seattle Genetics Says Adcetris Sets New Standard In Frontline Lymphoma" - Scrip, 20 Mar, 2018.)(Also see "ECHELON-2 Ushers In Another New Adcetris Indication For Seattle Genetics" - Scrip, 1 Oct, 2018.)*

'Our investors wanted to ensure that in parallel with us putting this first program into the clinic that we also had the funding to rapidly develop our follow-on programs and make them a clinical reality in the coming months.'

Johnson said Adcetris' regulatory success indicated its inventors "used the right linker and payload chemistry."

"It's one of the few that have delivered an approved product to date. It shows that to be success in this space you need the right combination of target, linker and payload. You can't go after the wrong target; you can't just be focused on using the most potent payload available; it must be the right combination of going after the right target with the right antibody and utilizing the right linker/payload chemistry," he said.

It all comes down to getting the correct balance when building ADC constructs, Johnson concluded.

"Lessons have been learned over recent years and some of the more potent payloads may be getting a bit tripped up in terms of safety outcomes in patients once they get into the clinic and that's something we've also tried to learn from."

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Korean Pharma Finds Own Way To Collaborative And Open Innovation

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Although South Korean pharma companies may not have the unique open and external innovation platforms of global pharma firms, they have nevertheless been accumulating their own experience and know-how in recent years, to devise R&D strategies that meet their needs and are suitable for their particular situations.

Pharma companies in the country have been more aggressively making strategic investments in bioventures and in new drug R&D in the past few years, while other domestic trends have included the industry's increasingly global research expansion, the emergence of biotech start-ups and alliances, as well as an increase in global licensing deals.

In the global arena, between 2012 and 2016, more than one-third of big pharma's in-licensing deals were in oncology, an overwhelming indication of the importance of this therapeutic area and the investment that large companies are making to find improvements over existing treatments and advance the standard of care, according to Datamonitor Healthcare's report titled "Big Pharma Licensing Trends, 2012-2016."

In addition, other therapy areas such as endocrine, metabolic, and genetic disorders, immunology/inflammation, and neurology also had stronger representations in the deal-making universe.

As far as major Korean pharmas are concerned, **Yuhan Corp.** and **Daewoong Pharmaceutical Co. Ltd.** shared some of their strategies and cases of successful open innovation at a recent Bio Open Plaza organized by the Korea Pharmaceutical and Bio-Pharma Manufacturers' Association (KPBMA) in Seoul.

YUHAN'S R&D STRATEGY

Yuhan has been increasing its strategic R&D investment since 2015, focusing on oncology and particularly immuno-oncology. Of Yuhan's current 22 R&D pipeline assets, 18 are in the oncology and metabolic disease areas, while projects that are progressing through some form of open innovation account for 55% of the total, noted Moo Young Song, research scientist at the company.

"Big pharmas are progressing about 50% of their pipelines with partners, and this trend is increasing. Licensing deals are focused on oncology and metabolic disease. Recently, CNS and rare disease deals have also been rising," Song observed.

Likewise, six of Yuhan's 11 strategic investment projects in new drug development programs are for oncology programs, including four in immuno- oncology.

"We came up with the internal strategy taking into consideration global and domestic trends. Domestically, pharmas are expanding global R&D and increasing alliances with biotech start-ups," Song said.

PURSUING OPEN INNOVATION

Based on such trends, Yuhan is aiming to reinforce its open innovation networks, focus on R&D in oncology and NASH (non-alcoholic steatohepatitis), increase its interest in CNS and rare diseases, facilitate the globalization of research, and explore "pharmerging" markets. "For us, early stage partnership is the key. We bring in early stage compounds from bioventures and add value to the drug compounds using our know-how and then license them out to third parties," he said.

Song cited the lung cancer program YH25448, an oral, potent, highly mutant-selective and irreversible third-generation EGFR tyrosine kinase inhibitor that penetrates the blood-brain barrier, which has been licensed in from Genosco, the US subsidiary of Korean venture Oscotec, as a successful example of pursuing external open innovation.

Results from an open-label, multi-center Phase I/II study with YH25448 (also known as GNS-1480) in patients with advanced non-small cell lung cancer with or without CNS metastases showed an objective response rate (ORR) of 64% for evaluable patients, an ORR of 67% for T790M-positive patients, 47% for T790M-negative patients, and 56% for patients with brain metastases.

The company aims to finish a Phase II study this year and then actively seek a global out-licensing deal.

SEEKING PARTNERS

To facilitate global clinical trial programs for its core new drug development projects and actively seek licensing deals, Yuhan is also establishing operations in the US. It set up a US headquarters for open innovation in San Diego this March and will set up another US office in Boston later this year.

"In summary, the key to open innovation is to find good partners that can maximize our capabilities," Song added.

Some of Yuhan's recent notable achievements on the alliances front include a $218m deal to license out the novel peptide drug for degenerative disc disease YH14618 (originally licensed in from Ensol Biosciences) to US-based Spine Biopharma, and the establishment of immuno-oncology joint venture **ImmuneOncia Therapeutics Inc.** with **Sorrento Therapeutics Inc.**

ImmuneOncia received an IND approval from South Korea's Ministry of Food and Drug Safety earlier this year to begin a Phase I study with IMC-001, a fully human anti-PD-L1 monoclonal antibody.

DAEWOONG'S STRATEGY

While Daewoong hasn't achieved as many successful external and open innovation alliances as Yuhan, it is gearing up to take such steps going forward, Jongsang Ryu, executive director of R&D at Daewoong Pharmaceutical, told the Seoul meeting.

Daewoong's strategy aims to focus mainly on the areas its pharma arm is good at, and to find partners that can complement its weaknesses.

"Regardless of company size, we are seeking a co-evolution and co-existence strategy. Open collaborations are quite active in South Korea and Daewoong is aiming to take a lead,"

CONTINUED ON PAGE 23

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

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

Selected clinical trial developments for the week 28 September–4 October 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Eli Lilly/Boehringer Ingelheim	*Jardiance* (empagliflozin) as insulin adjunct	type 1 diabetes	EASE; *Diabetes Care* online, Oct. 4, 2018.
Bayer/J&J	*Xarelto* (rivaroxaban)	secondary stroke prevention	NAVIGATE ESUS; *The Lancet Neurology*, Sept. 28, 2018.
Melinta Therapeutics Inc.	*Vabomere* (meropenem/ vaborbactam)	nosocomial pneumonia, septicemia, UTIs	TANGO 2; *Infectious Diseases and Therapy*, Oct. 1, 2018.
Bausch Health Companies Inc.	*Bryhali* (halobetasol propionate) lotion	psoriasis	Story 301, 302; *Journal of Drugs in Dermatology*, Oct. 2018.
Adamas Pharmaceuticals	*Gocovri* (amantadine)	Parkinson's disease	EASE LID; *Parkinsonism and Related Disorders*, online.
PHASE III INTERIM/TOP-LINE RESULTS			
Eli Lilly	*Ultra Rapid Lispro* (LY900014)	diabetes, type 1 and type 2	PRONTO-T1D, -T2D; met primary efficacy endpoints.
Merck & Co	*Delstrigo* (doravirine/ lamivudine/tenofovir disoproxil fumarate)	HIV/AIDS	DRIVE-SHIFT; met primary endpoint.
Seattle Genetics/ Takeda	*Adcetris* (brentuximab vedotin)	CD30-expressing peripheral T-cell lymphoma, frontline	ECHELON-2; achieved primary endpoint.
Duchesnay Inc.	*Osphena* (ospemifene)	vaginal atrophy	Efficacious, well tolerated.
Orphazyme A/S	arimoclomol	Niemann-Pick disease type C	Encouraging efficacy, well tolerated.
Sanofi	*MenACYW-TT* conjugate vaccine	meningococcal vaccine	MET56; immunogenic as booster dose.
Novo Nordisk	*Ryzodeg 70/30* (insulin degludec/aspart)	diabetes, type 2	Step-by-Step; once-daily dosing.
UPDATED PHASE III RESULTS			
Shionogi/ Roche Holding AG	baloxavir marboxil	influenza	CAPSTONE 2; reduced time to clinical improvement.
Vital Therapies Inc.	ELAD cell therapy	liver failure	Did not meet endpoints.
Radius Health	*Tymlos* (abaloparatide)	osteoporosis	ACTIVExtend; bone mineral density increased.
Foamix	FMX101 (minocycline) topical foam	acne, moderate-to-severe	FX2017-22; positive results.
Otonomy Inc.	*Otividex* (dexamethasone)	Meniere's disease	AVERTS-2; positive results.
Gilead Sciences/ Johnson & Johnson	*Symtuza* (darunavir/cobicistat/tenofovir alafenamide/emtricitabine)	HIV/AIDS	EMERALD; long-term efficacy of single daily tablet shown.
Gilead Sciences	*Biktarvy* (bictegravir/ emtricitabine/tenofovir alafenamide)	HIV/AIDS	Study 1489; Sustained efficacy long term.
ObsEva SA	nolasiban (OBE001)	reproductive disorder	IMPLANT2; increased live birth rate.
Achaogen	*Zemdri* (plazomicin)	urinary tract infections, septicemia	EPIC, CARE; high eradication rates.
Sanofi	*Zynquista* (sotagliflozin)	type 1 diabetes	inTandem2; effective as insulin adjunct.
Merck & Co	*Delstrigo* (doravirine/ lamivudine/tenofovir disoproxil fumarate)	HIV/AIDS	DRIVE-AHEAD; efficacy and safety confirmed.

Source: Biomedtracker | Informa, 2018

CONTINUED FROM PAGE 21

Ryu declared. The company is looking to beef up its new drug pipeline, particularly in anti-fibrosis agents, oral peptide drug delivery system technology, and stem cell platform technology. Its therapeutic focus areas are autoimmune disorders, fibrotic diseases, gastrointestinal, immuno-oncology, and cardio-metabolic, as well as neuroscience and pain.

Based on its differentiated technology, it aims to enter advanced markets with optimized partners. As an example, it cited its botulinum toxin product *Nabota*, which is poised to enter the US market via its partner **Evolus Inc.** In late August, Daewoong received an acceptance letter for the resubmission of a BLA to the US FDA for the botulinum toxin type A preparation after receiving a complete response letter earlier this year.

The company received regulatory approval for Nabota in Canada in August and expects to launch the product in that market in the first half of next year; Nabota is also going through a regulatory approval process at the EMA in Europe.

GEOGRAPHICAL EXPANSION

Daewoong, which is aiming to sharply grow its global business, has been actively expanding its overseas presence by setting up 10 branch offices abroad and boosting exports. "By region, we have been experiencing trial and error, and learning ways to bring changes and innovations," said Ryu.

Stem cell therapy is one area it is focusing on, and where it is developing through collaborations with Seoul National University and Kangstem Biotech. In 2015, Kangstem granted Daewoong the exclusive right to sell *Furestem* therapeutic stem cell products at home and abroad, and will also participate in R&D for follow-up indications.

By advancing into global markets, Daewoong has also been acquiring know-how that meets local specific culture and regulations. As an example, it set up a joint venture, PT Daewoong Infion, with Indonesia's PT Infion. It also established the Biotechnology Research Center UI-Daewoong via a collaboration with Universitas Indonesia.

"Initially, we couldn't penetrate into Indonesia's regulations. We needed a joint venture there. With the help of the Indonesian government, we established a JV and a new business of biologics manufacturing in the country," Ryu explained. "After the JV launched an EPO [erythropoietin] product in Indonesia, the product grabbed more than a 40% market share in just six months. Now, we are exporting the EPO to Korea. We call this reverse innovation."

He also cited Daewoong's acquisition of **HanAll BioPharma Co. Ltd.** in 2015 as a successful open innovation case, as two companies with different strengths merged and created synergies.

Although HanAll had various pipeline assets, it may not have reached licensing deals with good structures without the help of Daewoong. Late last year, HanAll BioPharma Co. licensed out the novel anti-FcRn antibody HL161BKN to Switzerland-based **Roivant Sciences GMBH** in a deal worth $525m plus sales royalties.

"These deals aren't just sizable in value, but they also have good structures. It is a good example of the merged pharma creating synergies," Ryu said.

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Jarlath Keating	ABL Inc	Chief Commercial Officer	MilliporeSigma	Vice President of Global Commercial Operations	26-Sep-18
Jesus M. Gonzalez Moreno	Destiny Pharma plc	Chief Medical Officer	TiGenix SAU	Global Clinical Development Director	26-Sep-18
X. Kate Zhang	Editas Medicine Inc	Vice President, Biological Development	Sanofi SA	Senior Director, Global translational science and biological pharmaceutical development	1-Oct-18
Yan Moore	Ipsen Group	Senior Vice President, Oncology Therapeutics	BioCancell Therapeutics	Chief Medical Officer and Senior Vice President, Research and Development	1-Nov-18
Ali Zeaiter	PharmaMar SA	Director, Clinical Development	Servier	Head, Clinical Development	1-Oct-18
Carsten Brunn	Selecta Biosciences	President and Chief Executive Officer	Bayer AG	President, Pharmaceuticals, Americas Region	1-Dec-18
Marino Garcia	Zealand Pharma AS	Senior Vice President, Corporate and Business Development	Synergy Pharmaceuticals Inc	Executive Vice President and Chief Strategy Officer	1-Oct-18

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

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