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Gilead/Kite Pricing For Yescarta Undercuts Novartis's CAR-T Kymriah

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Gilead Sciences Inc. paid $11.9bn for **Kite Pharma Inc.** in a deal that closed earlier this month and will soon reap rewards from that long-awaited transaction following the Oct. 18 US FDA approval of *Yescarta* (axicabtagene ciloleucel), but its return on investment won't come at a market-leading price.

The autologous CD19-targeting chimeric antigen receptor T cell (CAR-T) therapy was approved for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy and Gilead priced the one-time treatment at $373,000. While that's 21.5% lower than the $475,000 list price for **Novartis AG**'s *Kymriah* (tisagenlecleucel), which was the first CAR-T therapy approved by the FDA at the end of August, the initial Yescarta indication covers about 7,500 patients in the US versus about 600 for the pediatric acute lymphocytic leukemia (ALL) patients eligible for treatment with Kymriah.

David Chang, worldwide head of research and development and chief medical officer at Kite, said in an interview that the company's product pricing is "really based on what the Yescarta therapy brings to the patient population, which is really underserved with existing therapies."

Kite operates as a subsidiary of Foster City, Calif.-based Gilead and maintains its headquarters in Santa Monica, Calif. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" - Scrip, 29 Aug, 2017.)*

Jefferies analyst Michael Yee said in an Oct. 18 note about the Yescarta approval that he expects Gilead to see $200m to $250m in Yescarta revenue in 2018 – even with a slow initial rollout in a limited number of treatment centers. Consensus estimates are lower at more than $150m.

"One caveat is that [Gilead (GILD)] has suggested (and based on our channel checks on various centers) that the color in the market is that GILD may start the launch more carefully to ensure top centers do not run into safety issues. Therefore, while there may be an initial tepid/cautious launch, big picture we think first year sales will be very good," Yee wrote.

Chang isn't directly involved in pricing negotiations, so couldn't say what kind of discounts, rebates or alternative contracting will be applied to Yescarta's cost.

However, a Gilead spokesperson told *Scrip*: "We are in ongoing and active discussions with all commercial and government payers, and there are varying degrees of interest and ability to execute value-based agreements. We have communicated our openness to considering solutions that improve patient access."

KITE CONNECT

A service called Kite Connect will help patients and physicians track shipments and manufacturing of their individualized Yescarta therapies as well as assist patients with health insurance questions and connect them with third-party resources to assist with travel to treatment centers.

Yescarta involves removing T cells from patients via leukapheresis and shipping them to Kite's manufacturing facility in El Segundo, Calif. where the cells are genetically engineered to target cancer cells expressing the CD19 receptor. Kite sends patients' engineered cells back to their treatment center

CONTINUED ON PAGE 7

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

Business
Lilly's Billion-Dollar Deal With CureVac (p5)

Scrip Asks...
What's The Current Climate For Deal-Making? (p10)

Life In The Old Dog Yet
Dyslipidemia Market Growth Expected To 2025 (p12)

from the executive editor

alex.shimmings@informa.com

As Hallowe'en approaches, the third-quarter results season is firmly with us but the first companies to report have braved pharma's more common recurring nightmares to report solid figures.

Johnson & Johnson remains on track to drive above market annual growth, even without sirukumab, which has just received a US FDA complete response letter leading to filing withdrawals. Swiss major Roche, meanwhile, is managing to keep the biosimilar bogeyman at bay, for a while at least, through strong sales of its newer products including its latest offering, *Ocrevus* for multiple sclerosis. See pages 4 and 13 for more details.

The possibility of failure at Phase III always haunts drug companies and their investors, and last week the Grim Reaper came for Celgene's Crohn's disease candidate, mongersen. Continuation of development for the oligonucleotide product was deemed futile by the data monitoring committee for its main REVOLVE study. Page 8 has all the gory details.

The fears don't even stop once a product is safely past the regulatory approval stage. Obesity company Orexigen's dreams of reinvigorating its weight loss drug Contrave have turned to dust and the firm now fears for its future (p 16). Then there is the very real specter of antibiotic resistance (p 23).

But be of good cheer – All Hallow's Eve gives way to All Saints Day, and there is good news to savor in this issue. See pages 1 and 6 for successes for truly innovative drugs like Kite's *Yescarta* and GSK's *Strimvelis*. The darkest hour is always before the dawn.

Scrip

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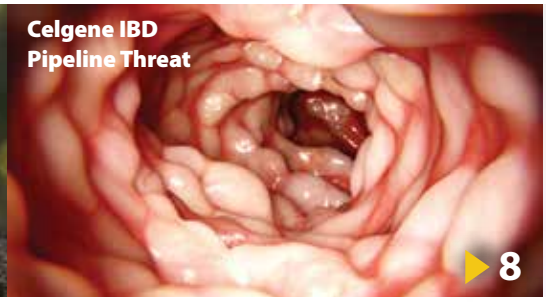

exclusive online content

Anthem In-House PBM Will Rely On CVS But Retain Formulary Control
http://bit.ly/2ylby1G
Hybrid approach to pharmacy benefit management expected to save insurer $4bn annually after Anthem ends its relationship with Express Scripts in 2020. Plans include "going out to the market and competing with the freestanding PBMs."

$500m And Counting: Vir Puts Big Money To Work In Infectious Diseases
http://bit.ly/2zvwckQ
Vir Biotechnology launched in January with $150m and a focus on infectious diseases. Now, the George Scangos-led venture has raised more than $500m and signed multiple collaboration agreements, including deals with Alnylam and Visterra worth as much as $1bn each.

Deal Watch: Syndax Gets Former Vitae Leukemia Program From Allergan
http://bit.ly/2zIP8h9
Cancer-focused biotech obtains preclinical program aimed at leukemia subset involving chromosomal rearrangements. Merck acquires an interest in KalVista and rights to its diabetic macular edema candidate, while Arcturus partners with Janssen in hepatitis B.

HemoShear's Human Disease Model Validated By Takeda NASH Deal
http://bit.ly/2yDgfMF
Emerging Company Profile: HemoShear thinks its REVEAL-tx platform can identify novel targets and validate drug candidates better than existing bench research methods. Japan's Takeda is betting in a new collaboration that HemoShear can deliver novel targets in NASH.

Ukraine Nod Paves Way For Panacea Sales To 49 Other Nations
http://bit.ly/2y0qIT6
Panacea Biotec has received another piece of good news as it strives to return to profit – this time from Ukraine which has awarded a GMP certificate to the Indian drug firm to supply 22 medicinal products to the country. It also opens up 49 other nations for the firm's products.

inside:

COVER / Gilead/Kite Pricing For Yescarta Undercuts Novartis's CAR-T Kymriah

4 J&J Immunology Growth Now Hinges On Stelara, Tremfya After RA Setback

5 Lilly's Billion-Dollar Deal With CureVac

6 GSK Bubble Baby Syndrome Gene Therapy Gets NICE Nod

6 Chi-Med's Savolitinib Overcoming Resistance

8 Celgene IBD Pipeline In Question As Mongersen Crohn's Disease Trial Ends

9 Opdivo Use For Urothelial Cancer Blocked By NICE In Draft Guidance

9 Consolidation in Generics As Impax And Amneal Merge

10 What's The Current Climate For Deal-Making? (Part 1)

12 Life In The Old Dog Yet: Growth In Dyslipidemia Market Expected To 2025

13 New Drugs Shine But Biosimilars Blunt Roche Revenue Rise

14 Lynparza Partners AZ And Merck & Co Target US Breast Cancer Market

16 If Orexigen Disappears, Who's Left In The Obesity Market?

18 Novo's Semaglutide: Retinopathy Warning Unlikely To Dim Commercial Prospects

20 Brexit Ambiguity A Top Priority For Bayer's New UK & Ireland CEO

21 Silence Seeks Share Of Alnylam RNAi Success In Legal Action

22 **Pipeline Watch**

23 UK R&D Centre for Antimicrobial Resistance Goes Into Battle

23 **Appointments**

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J&J Immunology Growth Now Hinges On Stelara, Tremfya After RA Setback

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Johnson & Johnson's pharmaceutical unit remains on track to drive above-market compound annual growth through 2021, even without one of the new drugs the diversified pharma had hoped to have on the market, worldwide chair-pharmaceuticals Joaquin Duato assured investors during the company's third quarter sales and earnings call on Oct. 17.

J&J announced in its quarterly release that it would withdraw global regulatory filings for the interleukin-6 inhibitor sirukumab for rheumatoid arthritis after the drug received a complete response letter from the US FDA in September. *(Also see "Keeping Track: An RMAT, Two QIDPs, And Some Bad News Too" - Pink Sheet, 24 Sep, 2017.)* The decision followed a vote against approval by the agency's Arthritis Advisory Committee in August over concerns about a mortality imbalance in clinical trials. *(Also see "Janssen's Sirukumab Falls On Mortality Concerns At US FDA Panel" - Pink Sheet, 2 Aug, 2017.)*

J&J's sirukumab collaborator **GlaxoSmithKline PLC** apparently saw the writing on the wall before the FDA rejection, having backed out of the partnership in July. *(Also see "J&J Prepares For US Sirukumab Launch After Regaining Rights From GSK" - Scrip, 26 Jul, 2017.)*

"Are we disappointed with sirukumab? We are, because we stand behind sirukumab and the value it has as an anti-IL-6," Duato said. "The additional data request that we were having from the CRL would have delayed the launch of sirukumab significantly, and based on the competition that exists there with the other IL-6s, we thought the best thing for us was to focus on other priorities."

Two IL-6 inhibitors already are on the market for rheumatoid arthritis, which only dimmed the prospects for sirukumab: **Roche**'s *Actemra* (tocilizumab) and **Sanofi** and **Regeneron Pharmaceuticals Inc.**'s *Kevzara* (sarilumab).

Sirukumab is one of the drugs J&J highlighted as a future growth driver during a briefing with investors in May to showcase its pharmaceutical portfolio. *(Also see "J&J Forges Ahead In Immunology Despite Competitive Dynamics" - Scrip, 18 May, 2017.)* Management promised at the time that the company would achieve its five-year growth goal even as it expects sales for its immunology workhorse *Remicade* (infliximab) to come under growing pressure from new competition, including biosimilars.

J&J largely has defended Remicade successfully in the US against the first biosimilars, **Pfizer Inc.**'s *Inflectra* (infliximab-dyyb) and **Merck & Co. Inc.**'s *Renflexis* (infliximab-abda), when it comes to market access, but the company has had to offer steeper discounts in exchange. *(Also see "J&J Immunology President On Remicade, Inflectra And The Art Of Contract Negotiations" - Scrip, 11 Oct, 2017.)* Sales of Remicade declined globally 7.6% to $1.65bn in the third quarter.

The setback with sirukumab puts more pressure on J&J's new psoriasis drug *Tremfya* (guselkumab), an IL-23 blocker, to drive growth, along with the established blockbuster *Stelara* (ustekinumab), approved for psoriasis, psoriatic arthritis and Crohn's disease. Stelara was cleared for a new psoriasis indication in adolescents 12 and older on Oct. 13, an important new target population, according to J&J, because one-third of individuals with plaque psoriasis are diagnosed before the age of 20.

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Johnson & Johnson's pharmaceutical unit is on track

Tremfya, meanwhile, joined the competitive psoriasis category following the FDA's approval in July. *(Also see "J&J's First-In-Class Tremfya Poised To Join A Crowded Psoriasis Market" - Scrip, 14 Jul, 2017.)* J&J said 3,000 physicians have prescribed the drug to some 9,000 patients since the launch.

Nonetheless, Duato hinted at some market access hurdles. "This is a very competitive market in this category," he said when asked by an analyst about payer acceptance. "We feel confident that we will have appropriate access moving into 2018."

Tremfya and Stelara remain pillars of the company's strategy in immunology, Duato said.

Sirukumab isn't the only setback J&J revealed with its third quarter financial report. The company said it has also discontinued a late-stage clinical trial testing talacotuzumab in patients with acute myeloid leukemia. Talacotuzumab is an antibody developed with technology licensed from **Xencor Inc.**, though J&J did not provide any details about why it discontinued the trial other than to say the decision was based on the "benefit/risk" profile.

But Duato turned the focus to apalutamide, a next-generation androgen receptor inhibitor the company filed with the FDA for the treatment of non-metastatic castration resistant prostate cancer that could extend J&J's prostate cancer franchise beyond *Zytiga* (abiraterone). *(Also see "J&J Hopes To Reach Market First For Pre-Metastatic Prostate Cancer With Apalutamide" - Scrip, 11 Oct, 2017.)* Another potential growth driver he highlighted was esketamine for treatment-resistant depression, which the company plans to file in 2018.

J&J's pharmaceutical sales increased 15.4% in the third quarter to $9.7bn, benefiting from the acquisition of **Actelion Pharmaceuticals Ltd.**, which contributed 7.9% to global operational sales growth. The Stelara and the oncology medicines *Darzalex* (daratumumab) and *Imbruvica* (ibrutinib) also contributed to the sales growth.

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Lilly's Billion-Dollar Deal With CureVac

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Cancer vaccine research has suffered clinical-stage setbacks over the years, but there have been suggestions that combining them with checkpoint inhibitors and other new anticancers has promise. That's cause enough for Germany's mRNA-focused biotech **CureVac AG** to attract its second big pharma collaborator, **Eli Lilly & Co.**, for its immunotherapy research.

Other potential reasons include the backing of SAP software company founder Dietmar Hopp and the Bill & Melinda Gates Foundation, which have both invested in Tubingen-based CureVac, and a line-up of other collaborators that include **Boehringer Ingelheim GMBH,** with which the biotech is collaborating on potential non-small cell lung cancer (NSCLC) vaccine research.

Also, in its second research focus, the development of prophylactic vaccines for infectious diseases, CureVac has attracted as collaborators, **Sanofi Pasteur** and IAVI (the International AIDS Vaccine Initiative). The company also has a GMP-compliant manufacturing facility able to make its chemically unmodified, self-adjuvanted complexed mRNA products in commercial-scale quantities.

But that's not to say CureVac's cancer vaccine research has had a smooth ride so far. In Jan. 2017, the company reported disappointing results in a Phase IIb study involving a potential prostate cancer vaccine, CV9104. The vaccine had no effect on overall survival or progression-free survival in prostate cancer patients, and that's when CEO Ingmar Hoerr said he saw the path forward would involve the use of its *RNActive* cancer immunotherapy in combination with checkpoint inhibitors.

CureVac is now concentrating on a combining its approach with checkpoint inhibiting antibodies in other cancer types, such as in its collaboration with Boehringer Ingelheim in NSCLC.

Lilly has agreed to pay an upfront of $50m and to take an equity stake worth €45m in CureVac in order to collaborate with the European biotech on up to five potential cancer vaccines based on CureVac's proprietary RNAactive technology, in different tumor types; CureVac could also receive more than $1.7bn in development and commercialization milestones if all five vaccines are developed, plus tiered royalties on product sales.

The companies did not disclose the cancers they would be working on. Lilly's Greg Plowman, vice president of oncology research, said the technology, "could potentially be the next frontier of cancer medicines," in a company statement issued on Oct. 18. That matches up with Lilly's research strategy – the US big pharma targeted "next-generation immunotherapies" as a research area of future interest in the revision of its R&D strategy earlier this year. *(Also see "Lilly Hopes To Revitalize Its Cancer Brand With 'Foundational' Agents" - Scrip, 25 Jul, 2017.)*

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GSK Bubble Baby Syndrome Gene Therapy Gets NICE Nod

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Babies in England born with an ultra-rare immune deficiency condition will soon be able to travel to Italy and be treated with **GlaxoSmithKline PLC**'s gene therapy *Strimvelis*, with the costs covered by the National Health Service.

The National Institute for Health and Care Excellence has published draft guidance recommending Strimvelis as an option for treating severe combined immunodeficiency due to adenosine deaminase deficiency, or ADA-SCID. The inherited genetic condition, also known as bubble baby syndrome, affects the body's white blood cells, leaving children without a fully-functioning immune system and extremely vulnerable to infections.

The current treatment is a stem cell transplant, but closely-matched donors are hard to find and the transplants may not be successful in all cases – they also carry a risk of mortality and graft-versus-host disease. Those not receiving treatment need to be kept in isolation, hence the bubble baby reference.

Now NICE, applying its new cost effectiveness limits for treatments for very rare conditions for the first time, is recommending Strimvelis when no suitable stem cell donor is available. The cost watchdog notes that around three babies a year in England are born with ADA-SCID.

Strimvelis, which was approved in May 2016, is a gene therapy in which a patient's bone marrow cells are removed and modified outside the body to produce working ADA enzyme. The modified cells are then returned to the patient via an infusion drip into a vein.

The cost is €594,000 but NICE believes it meets its cost-effectiveness criteria as the treatment is usually given once only and the effects are thought to be life-long. Strimvelis, which was developed in partnership with Fondazione Telethon and Ospedale San Raffaele, has to be administered at a hospital in Milan but travel to have the treatment will be paid for as part of the care package provided by the NHS.

NICE says that during its review, it heard from experts who considered that having the option of Strimvelis "would be life-changing for patients and that improvements to the quality of life of carers occurred immediately after a successful treatment." Carole Longson, director of the centre for health technology assessment at NICE, added in a statement that treatment with Strimvelis means that children born with ADA-SCID "will now have a better chance of being able to lead as near normal a life as possible, going to school, mixing with friends, free from the constant threat of getting a potentially life-threatening infection."

Despite the high price tag, Strimvelis is clearly not going to be a big earner for GSK given the thankfully tiny patient population. The UK giant announced that the first patient was treated in March, almost a year after it was approved for sale – the company has estimated that ADA-SCID affects about 15 children per year in Europe.

The approval was based on data which showed a 100% survival rate at three years post-treatment with Strimvelis for all children in the pivotal study (n=12) and every child receiving the treatment who contributed to the marketing authorization data package was alive in May 2016 (n=18), with a median follow-up duration of approximately seven years.

Strimvelis is only the second gene therapy for an inherited disease to be licensed anywhere in the world. The other was **uniQure NV**'s *Glybera* (alipogene tiparvovec) for familial lipoprotein lipase deficiency but the treatment, which famously came with a $1m price tag and was only used on one patient, was discontinued earlier this year. *(Also see "White Flag Raised: UniQure Gives Up On Glybera, But Not Gene Therapies" - Scrip, 21 Apr, 2017.)*

Across the Atlantic, **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec) for a rare inherited blindness, looks set to become the first US gene therapy following a unanimous positive FDA advisory committee review last week. *(Also see "Spark's Gene Therapy Is On The Cusp Of Approval; Now It Gets Interesting" - Scrip, 12 Oct, 2017.)*

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Chi-Med's Anticancer Shows Promise In NSCLC

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AstraZeneca PLC and its China-based partner **Chi-Med** (**Hutchison China MediTech Ltd.**) have highlighted preliminary clinical evidence that the addition of the investigational agent, savolitinib, to other anticancer therapies may be of clinical benefit in certain non-small cell lung cancer (NSCLC) patients whose tumors have become resistant to therapy.

Patients with epidermal growth factor receptor (EGFR) mutation-positive advanced NSCLC can experience disease progression through a process called MET amplification, a difficult-to-treat anticancer resistance mechanism, for which new means of treatment are required. Savolitinib, discovered by Chi-Med researchers, is an orally-active selective inhibitor of c-MET (mesenchymal epithelial transition factor) receptor tyrosine kinase, and is potentially a first-in-class agent for this unmet clinical need.

Analysts at Deutsch Bank have characterized the second-half of 2017 as an important time for clinical readouts from Chi-Med's product pipeline, which is based on a strategy of developing more selective inhibitors against validated targets with better safety and tolerability. And lung cancer is not the only condition in which savolitinib may be beneficial. Chi-Med and AstraZeneca have just started the SAVOIR Phase III study in c-MET driven papillary renal cell carcinoma, after promising early-stage findings. *(Also see "Pipeline Watch: Phase III Progress With Anacetrapib, ALKS 3831 And LentiGlobin" - Scrip, 30 Jun, 2017.)*

Savolitinib is also in earlier-stage evaluation for clear cell renal carcinoma and gastric cancers, as monotherapies and in combination with other agents.

Impax and Amneal claimed that nearly half of all pipeline products are "exclusive first-to-file, first-to-market or other high-value opportunities."

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CONTINUED FROM COVER

where the therapy is infused into the patient to attack leukemia cells.

"In our pivotal study, the time from leukapheresis to the product being in the clinic was 17 days and that's the target as we launch the product commercially," Chang said. The 99% manufacturing success rate in the pivotal Phase II ZUMA-1 clinical trial also is Kite's goal for Yescarta in the commercial realm.

Novartis' Kymriah also is a CD19-targeting CAR-T therapy and the turnaround time for manufacturing the product is expected to average 22 days. Kite, now that it's owned by Gilead, may be able to speed up Yescarta's administration to patients by establishing additional manufacturing sites.

"As time goes on, especially now that we are a Gilead company, we are already beginning to evaluate building additional manufacturing facilities," Chang said. He noted that Kite is evaluating sites elsewhere in the US and in Europe, where a marketing authorization application (MAA) for Yescarta is under review and an approval decision is expected in the first half of 2018. The European Medicines Agency (EMA) granted a Priority Medicines (PRIME) designation to potentially speed the product through the EMA approval process. *(Also see "Kite First Off The Blocks For EU CAR-T Filing" - Scrip, 1 Aug, 2017.)*

The Yescarta US label covers patients with diffuse B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), high-grade B-cell lymphoma and transformed follicular lymphoma (TFL) – similar to the population in the ZUMA-1 trial that supported the therapy's approval. The therapy is not indicated for patients with primary central nervous system lymphoma.

Chang said Kite is pleased with the speed of the FDA's approval – Yescarta's PDUFA date was Nov. 29, but Novartis' Kymriah also was approved a little more than a month before its action date – and with the agency's decision to grant full approval based on the mid-stage study rather than an accelerated approval that would require an additional study to clinch full approval. Kite's therapy also was approved without an advisory committee meeting. *(Also see "Kite's Axi-Cel CAR-T: No Adcomm, No Problem" - Pink Sheet, 11 Aug, 2017.)*

"This approval demonstrates the continued momentum of this promising new area of medicine and we're committed to supporting and helping expedite the development of these products," FDA commissioner Scott Gottlieb said in the agency's statement announcing Yescarta's approval. "We will soon release a comprehensive policy to address how we plan to support the development of cell-based regenerative medicine. That policy will also clarify how we will apply our expedited programs to breakthrough products that use CAR-T cells and other gene therapies. We remain committed to supporting the efficient development of safe and effective treatments that leverage these new scientific platforms."

STRONG EFFICACY WITH A SAFETY TRADE-OFF

The overall response rate in ZUMA-1 was 72% of the 101 patients enrolled in the study and 51% achieved complete remission with no detectable cancer. The remarkable efficacy came with early, severe side effects, however, with 13% experiencing Grade 3 or higher cytokine release syndrome (CRS) and 31% experiencing neurological toxicities. Neurological toxicities observed to date with Yescarta include a death from cerebral edema in a ZUMA-1 extension study. *(Also see "Too Sick For CAR-T? Kite Reports Cerebral Edema Death" - Scrip, 8 May, 2017.)*

Like Kymriah, the Kite CAR-T therapy was approved with a boxed warning about CRS and neurological toxicities and the label carries a Risk Evaluation and Mitigation Strategy (REMS) that requires physicians to be trained about Yescarta's risks and certified to administer the CAR-T therapy.

Kite already has a team working on training treatment centers and expected to have 16 centers certified by the time of Yescarta's approval. The Gilead subsidiary is actively training 30 additional centers with the goal of certifying 70 to 90 centers across the US. Chang said Kite's commercial team has been preparing for Yescarta's launch for two years and the product could be administered to the first commercial patient at a certified treatment center in a matter of weeks.

The safety requirements for Yescarta and Kymriah are similar and the products' pricing may be similar after factoring in discounts under Novartis' reimbursement agreements. *(Also see "Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval" - Scrip, 31 Aug, 2017.)* The company is negotiating value-based contracts under which payers don't pay for Kymriah if pediatric ALL patients don't respond during the first month after treatment. The response rate in the therapy's pivotal trial in pediatric ALL was 83% at three months, but response rates vary based on the type of cancer treated.

The Swiss big pharma's senior vice president and global head of oncology strategy and business development Pascal Touchon said at a recent cell and gene therapy conference that "every indication will lead to a different type of [pricing] approach." *(Also see "Cell And Gene Therapies: Where Few Standard Rules Apply" - Scrip, 6 Oct, 2017.)*

MORE INDICATIONS COMING SOON

Both Kite and Novartis also are studying their first CAR-T therapies in multiple indications.

Pivotal trials are under way for Yescarta in mantle cell lymphoma (MCL), adult ALL and follicular lymphoma. "We are expecting that those studies will be complete sometime in 2018 enabling us soon after to seek additional indications," Chang said. He also noted that Kite is studying the treatment in earlier-stage DLBCL after patients failed just one prior therapy.

"With two products – two engineered cell therapies – being approved within the last few months, I think this is a really exciting time for cell therapy," Chang said. "Having been in this field for three or four years, I can say this is just the beginning."

The impact of Gilead's Kite acquisition and the first CAR-T therapy approvals will be felt throughout the cell and gene therapy field. Already, companies developing cell therapies have seen investor interest and their values rise. *(Also see "Rising Tide Lifts All CAR-T Ships After Gilead/Kite Deal, Kymriah Approval" - Scrip, 4 Sep, 2017.)*

Jefferies analyst Yee noted three upcoming milestones for the CAR-T field that could impact Yescarta's competitive position: safety findings in pivotal Phase IIb data for **Juno Therapeutics Inc.**'s JCAR017 in non-Hodgkin lymphoma, which are due in the second half of 2018; pricing for Kymriah's DLBCL indication, which is expected to win FDA approval in the second half of 2018; and Phase I efficacy for the allogeneic CD19-targeting CAR-T therapy UCART19 from **Cellectis SA** and partner **Pfizer Inc.** *(Also see "Pfizer Picks 'Off-The-Shelf' CAR-T And Backs TALEN Over CRISPR" - Scrip, 19 Nov, 2015.)*

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Celgene IBD Pipeline In Question As Mongersen Crohn's Disease Trial Ends

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Celgene Corp.'s hope of becoming an inflammation and immunology leader is being threatened as it pulls the plug on two studies evaluating mongersen for the treatment Crohn's disease at the recommendation of the trial's independent data monitoring committee.

Widely known for its oncology therapies *Revlimid* (lenalidomide) and *Pomalyst* (pomalidomide), Celgene's foray in the inflammation and immunology segment had been drawing attention as it explored three oral drugs: *Otezla* (apremilast), ozanimod, and mongersen (formerly GED-0301), each with different mechanism of action in inflammatory bowel disease (*see box*). Celgene has been hoping to use these research efforts to establish a position in the underserved areas of Crohn's disease and ulcerative colitis. *(Also see "Celgene Sets Sights On Becoming Inflammation and Immunology Power Player" - Pink Sheet, 20 Jul, 2015.)*

But that aspiration was knocked on the head on Oct. 19 when Celgene said that after consulting the data safety and monitoring committee that was overseeing the main mongersen study, called REVOLVE, it had decided to stop developing the drug.

It cited a futility analysis, implying the medicine was not effective, but said there were no safety problems.

Celgene said it will now assess whether to continue its clinical program for mongersen. But in a brief statement Celgene gave no details on how mongersen fared in the Phase III REVOLVE or Phase III SUSTAIN extension trials. Celgene has also been developing mongersen in combination with ozanimod.

Celgene is abandoning its Phase III DEFINE trial, which like REVOLVE had been intended to assess mongersen in Crohn's disease, and that the biotech will now study the full dataset from a Phase II study evaluating mongersen in ulcerative colitis to determine what to do next.

Striking a hopeful note, Scott Smith, president and chief operating officer, stated that Celgene remains "committed to advancing our portfolio of novel medicines for patients suffering from this disease and other inflammatory bowel disorders."

FAILURE SEEN HAVING WIDE IMPACT

But some analysts warned the failure of mongersen in Crohn's disease has wide ramifications.

Analysts at Baird Equity Research said that "while the loss of one of the company's most advanced and high-profile pipeline programs is, in and of itself, disappointing, we believe the announcement will have a broader impact of calling into question the value of the rest of the pipeline."

Mongersen has been one of Celgene's most emphasized pipeline assets, and was a cornerstone of its move into inflammation and immunology. The medicine was bought in April 2014 for $710m from **Nogra Pharma Ltd.**, a private Irish company based in Dublin, and had been widely viewed as a potential blockbuster. Celgene at the time said that if the drug moved through development and was approved, Nogra would get another $815m, plus tiered sales milestones that could pass $1bn. *(Also see "Deal Watch: Much Activity Beyond GSK/Novartis/Lilly Pacts And Valeant/Allergan Bid" - Pink Sheet, 28 Apr, 2014.)*

Though Celgene is awaiting data on mongersen's impact on ulcerative colitis, some analysts believe the drug's target SMAD has more mechanistic rationale in Crohn's disease, leaving little hope for mongersen's commercial prospects.

"With the opportunity now gone – and Otezla arguably unable to pick up slack due to recent measures taken to boost demand – we believe ozanimod will have to outperform already-high commercial expectations," the Baird analysts said in a reaction note.

Analysts at Bernstein concurred, saying in a note that "with no clarity if the failure is due to something specific to Crohn's disease, or the drug, it is inherently a very high-risk program."

"With the ozanimod program advancing, we expect that unless results in ulcerative colitis are fantastic, the [mongersen] program would be discontinued," they concluded.

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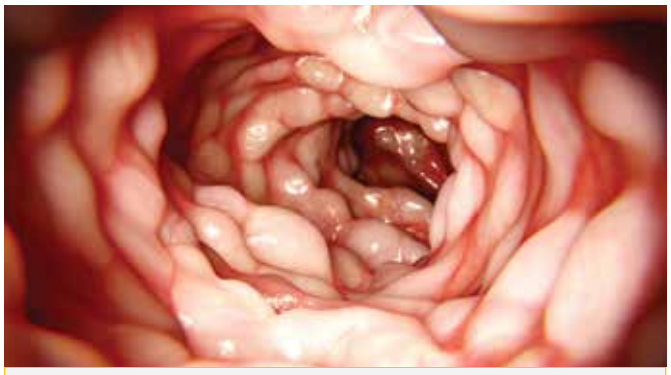

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Celgene's I&I Programs

Mongersen is an oligonucleotide that decreases a protein called Smad7 that is abnormally high in Crohn's disease. High levels of Smad7 interfere with an anti-inflammatory pathway in the gut called TGF-β1, which leads to increased inflammation.

Ozanimod is a novel, selective, sphingosine 1-phosphate 1 (S1PR1) and 5 (S1PR5) receptor modulator in development for immune-inflammatory indications including relapsing multiple sclerosis, ulcerative colitis and Crohn's disease. Selective binding with S1PR1 is believed to inhibit a specific subset of activated lymphocytes from migrating to sites of inflammation. The result is a reduction of circulating T and B lymphocytes that leads to anti-inflammatory activity, according to Celgene.

Otezla is a small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels which is thought to indirectly modulate the production of inflammatory mediators.

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Opdivo Use For Urothelial Cancer Blocked By NICE In Draft Guidance

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In draft guidance, England's health technology appraisal body NICE has decided against recommending **Bristol-Myers Squibb Co.'s** *Opdivo* (nivolumab) as an option for people who have advanced urothelial cancer and have already had platinum-containing chemotherapy treatment.

NICE said that while the drug is "likely to extend people's lives by more than 3 months," Opdivo has not been directly compared with other treatments in a clinical setting. "Based on the available evidence, it is difficult to establish the magnitude of the clinical benefit for nivolumab compared with current clinical practice," it said in an Oct. 20 statement.

BMS is struggling against the same barriers preventing its biggest programmed cell death protein-1 (PD-1) competitor, **Merck & Co. Inc.'s** *Keytruda* (pembrolizumab), from being used routinely on the National Health Service (NHS). NICE rejected Keytruda in draft guidance earlier this year for the same indication Opdivo is after.

BMS submitted data to NICE from two Phase II, single-arm trials: CheckMate 275 and CheckMate 032. The trials included 270 patients with locally advanced urothelial carcinoma with disease progression or recurrence after treatment with at least one platinum-containing agent, and 78 patients with carcinoma of the renal pelvis, ureter, bladder or urethra and disease progression after treatment with platinum-containing chemotherapy.

NICE argued that while the CheckMate studies provided efficacy estimates for Opdivo, they did not include randomized controlled trial evidence.

The watchdog also noted that it has already considered a confidential patient access scheme presented by BMS – however, it has still rejected the drug for routine use on the NHS. The committee said Opdivo "does not appear to have the potential to be cost effective."

Opdivo met NICE's criteria to be considered a life-extending end-of-life treatment, but the "most plausible estimate" of the incremental cost-effectiveness ratio (ICER) was £76,000 per quality-adjusted life year gained, which is higher than what NICE normally considers acceptable for end-of-life treatments. Life expectancy for people with urothelial carcinoma is less than 24 months and for patients with advanced or metastatic disease overall survival is much less than 24 months.

> Opdivo does not appear to have the potential to be cost effective

Adding to the disappointment for BMS, NICE has also rejected Opdivo for use on the Cancer Drugs Fund – a separate source of funding for cancer drugs in England – in the second-line urothelial cancer setting.

Urothelial cancer is the seventh most common cancer in the UK; approximately 10,000 people are diagnosed with the disease each year. There is a significant unmet need for second-line therapies for patients with urothelial cancer. Treatment options for people with disease progression after platinum-containing chemotherapy include docetaxel, paclitaxel or best supportive care. However, none of these treatments offer lasting benefit.

Clinical experts noted in the NICE consultation that there have been no new treatments for locally advanced or metastatic urothelial carcinoma for a number of years and that, unlike for other cancers, there is no targeted or personalized treatment yet available.

NICE's draft guidance is open for comments and the committee will next discuss Opdivo in urothelial cancer at a second appraisal meeting on Nov. 23, 2017.

This is not the first time BMS has failed to convince NICE to reimburse its drug; Opdivo's high cost has caused it issues in other indications. In Sept. this year, the HTA body approved Opdivo for use in England via the Cancer Drugs Fund as a treatment for non-small-cell lung cancer. However, this decision came after the PD-1 inhibitor was initially rejected by NICE for routine use on the NHS. *(Also see "UK's NICE Backs BMS's Opdivo In Lung Cancer, But Only Via CDF With Price Cut" - Pink Sheet, 20 Sep, 2017.)*

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Impax Merges With Amneal In Generics Link-Up

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The US generics market is to get another major player as **Impax Laboratories Inc.** and **Amneal Pharmaceuticals LLC** have confirmed that they are to merge.

The companies have agreed an all-stock deal that will give Impax shareholders 25% of a new, publicly traded company, which will use the Amneal name. Closely held Amneal, co-founded by brothers Chintu and Chirag Patel in 2002, will hold the remaining 75% in the combined company which will have 2017 pro forma net revenues in the range of $1.75-$1.85bn.

The deal will create the fifth-largest generics company in the US with 165 differentiated product families marketed in all dosage forms and holding a number one or two position "in a significant number of its marketed products," the new partners said in a statement. They also noted that the combination is expected to create one of the largest generic pipelines in the US, with about 150 pending abbreviated new drug applications (ANDAs) and 165 projects in active stages of development.

Impax bought 15 generics and a host of pipeline opportunities from **Teva Pharmaceutical Industries Ltd.** for $586m in June last year as part of the latter's antitrust requirements related to its own $40.5bn acquisition of **Allergan Inc.**'s generics business. The deal also gave Impax full rights to a generic of **Johnson & Johnson**'s ADHD drug *Concerta* (methylphenidate hydrochloride), which was approved by the US Food and Drug Administration in July this year. *(Also see "Teva Continues Divestitures To Close Allergan Deal With Sale To Impax" - Scrip, 21 Jun, 2016.)*

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http://bit.ly/2i2kQxB

What's The Current Climate For Deal-Making? (Part 1)

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Gilead Sciences Inc.'s recent buy-out of **Kite Pharma Inc.** for $11.9bn to supercharge its cancer pipeline ended a long period of speculation about what Gilead would do with its stockpile of cash – and set off a new round of speculation about the state of the deal-making environment across the biopharma industry.

Scrip asked a cross-section of people in the industry – from large and small companies, market analysts and other industry observers – what they make of the current climate for deal-making. Here, in their own words, are the responses from the biotech sector, defined here as smaller, clinical-stage firms. Part two will provide the responses from big pharma and other respondents.

HAVING THEIR SAY:

Biotech: Epizyme Inc., Erytech Pharma SA, Kura Oncology Inc., Zavante Therapeutics Inc., CytomX Therapeutics Inc., Fortress Biotech Inc., CANbridge Life Sciences Ltd., Athersys Inc., Corbus Pharmaceuticals Holdings Inc.

SUSAN GRAF, CHIEF BUSINESS OFFICER, EPIZYME

The current deal-making environment is a positive one-two punch for biopharma. First, today's equity climate is fueling biopharma companies in their work to discover and develop innovative therapies. Second, big pharma companies continue to need promising new assets to fill their pipelines.

This exciting combination creates a variety of options for biopharma companies as they consider the best way to add more value to their companies, while continuing to do what they do best: innovating new medicines, particularly in areas of large unmet patient need.

Susan Graf

Jean-Sebastien Cleiftie

Troy Wilson

Ted Schroeder

JEAN-SEBASTIEN CLEIFTIE, CHIEF BUSINESS OFFICER, ERYTECH

Our perspective on the current climate: although not at the level of 2015, 2017 year-to-date biotech deal-making levels have been robust, especially when we look at licensing in oncology, immuno-oncology and immunology, which will continue to drive transaction activity.

Biotech M&A levels have been contained through the summer, although one transaction can have a dramatic effect on deal statistics, as shown by the recent acquisition of Kite Pharma by Gilead. Furthermore, Q4 is generally an active quarter for deal making, so all in all it is too early to predict what 2017 will look like on the M&A front.

TROY WILSON, CEO, KURA ONCOLOGY

Although uncertainty around tax reform and drug pricing remains, we continue to see a constructive deal-making environment for biopharma. Companies and investors continue to seek deal premiums, and buyers appear to be exercising discipline. Large pharma are willing to pay a premium when products have been significantly de-risked while smaller companies must compete aggressively as they look to challenge the incumbents.

As a result, we are seeing companies such as **Incyte Corp.**, **Tesaro Inc.**, **Clovis Oncology Inc.** and others begin to expand their scope and become strategic partners in their own right. In general, it makes for a pretty healthy biopharma ecosystem.

TED SCHROEDER, PRESIDENT AND CEO, ZAVANTE THERAPEUTICS

I would characterize the current deal climate as active, but cautious. I find the current situation interesting for two reasons 1) Money is still relatively cheap and 2) Most companies remain under-valued. While I don't have great insight into the minds of big pharma, this feels more like a slowdown as they integrate their previous acquisitions and they assess what is going to happen with pricing and reimbursement.

Allergan PLC's shift to deals that are accretive in the short term (e.g. aesthetics) likely gives the rest of the players the sense that they don't have to be quite so aggressive for therapeutic deals. *(Also see "Allergan Adds Accretive Aesthetics Assets In $2.9bn LifeCell Acquisition" - Scrip, 21 Dec, 2016.)* Novel oncology assets still seem to be in high demand. Big pharma and biotech still need to fill their pipelines so I expect a steady deal flow going forward, but perhaps not quite like 2016.

DEBANJAN RAY, CFO AND HEAD OF CORPORATE DEVELOPMENT, CYTOMX

We find the current biopharma deal-making environment to be strong. Our recent interactions with pharma suggest that these companies value innovation, and are willing to think creatively to access innovative programs and platforms that have the potential

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to make a difference for patients.

In the past 18 months, we've closed collaborations with **AbbVie Inc.**, **Bristol-Myers Squibb Co.** and **Amgen Inc.** In these collaborations, our partners have been willing to structure deals that bring value to CytomX in the near term and the long term – for example, retention of certain development responsibilities and profit splits on certain products. This sort of creativity in deal structuring is highly valued by biotech companies such as CytomX, and tend to result in more productive collaboration discussions between biotech and pharma.

LINDSAY ROSENWALD, CEO, FORTRESS BIOTECH

I think the climate is as good as it's ever been. There's a great feel of demand for novel drug therapies in big pharma, big biotech, specialty pharma and even mid-sized and smaller companies so it all looks good right now. Which is always scary, right?

When I go to conferences, they're very crowded with lots of inquiries, lots of interest and it's like a bazaar, there's so many people interested in so many different programs. If you look at the announcements of all the deals, it seems there's a good volume of them.

From my perspective, because we're involved in lots of different technologies, lots of different companies, there is certainly a lot of interest from all parts of the industry and it seems like the demand for novel agents addressing unmet medical needs – I've never seen the demand as great as it is right now.

JAMES XUE, FOUNDER, CHAIR AND CEO, CANBRIDGE LIFE SCIENCES

We are very optimistic about the current deal-making environment in the biopharma industry, which has seen historic inflows of capital over the last five years and a record number of IPOs. With that influx of capital, exciting new therapeutic candidates have received much needed initial funding to support their advancement. However, capital market access for follow-on offerings has become somewhat more challenging since the peaking of sector performance in 2015. We believe this creates a very favorable environment for deal-making, as companies look to identify alternative funding sources.

Our particular model is to identify validated Western drug candidates for development and commercialization in China and northern Asia. In this sector, we are observing a rise in cross-border transactions between Western and Chinese companies, such as the recently announced agreement between **Celgene Corp.** and **BeiGene (Beijing) Co. Ltd.** *(Also see "Celgene Eyes IO Growth With BeiGene China Pact" - Scrip, 6 Jul, 2017.)* These types of deals can allow companies access to markets not otherwise easily accessed, as well as additional non-dilutive capital, which we believe will continue to make them attractive and a growing component of the environment.

Debanjan Ray

Lindsay Rosenwald

James Xue

Gil Van Bokkelen

Yuval Cohen

GIL VAN BOKKELEN, CEO, ATHERSYS

There is substantial interest in technologies that have the potential to address areas of significant unmet medical need, and we believe that will continue to be the case. This is especially true for innovative technologies targeted at indications that are related to the unprecedented demographic transition now occurring, with the large increase in the number of people age 65 and older as the baby boom generation gets older. This will have a massive global impact on health care, since there are quite a few diseases and conditions that will become more prevalent as the global population ages.

Unfortunately, many of these conditions currently lack effective treatment solutions, and for the patients that may mean institutional care, family care or professional home health care, and most families and societies around the world are simply unprepared for that. That need creates opportunities for innovative companies developing safer and more effective treatment solutions that can help improve quality of life for patients.

YUVAL COHEN, CEO, CORBUS

There has been a real drought in deals this year and so the recent Gilead/Kite deal was a very welcome change in that. It is probably too soon to see whether that was the start of a change or a one-off. What we've been hearing from big pharma is that there is real concern over high valuations of late-stage public companies that could be targets, but that is always counteracted by the ever-present need of big pharma for novel promising drugs in their pipelines. My feeling is that we will see a return to robust M&A activity shortly but perhaps more on the earlier (hence less expensive) side.

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For part 2 click here:
http://bit.ly/2iuW1hM

Life In The Old Dog Yet: Growth In Dyslipidemia Market Expected To 2025

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The dyslipidemia market may be old but there's room for growth

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The profound change in dynamics of the dyslipidemia market set in train by the loss of patent protection for *Lipitor* (atorvastatin) in 2010 continues as **AstraZeneca PLC**'s *Crestor* (rosuvastatin) and **Merck & Co. Inc.**'s *Zetia* (ezetimibe) and *Vytorin* (ezetimibe and simvastatin) follow it over the cliff. But the sector is not set for contraction yet – expensive new therapies should keep it buoyant out until 2025 at least.

Datamonitor Healthcare forecasts total antidyslipidemic sales revenues to increase over the forecast period in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) from $11.9bn in 2016 to $33.8bn in 2025, at a compound annual growth rate of 12.3%.

The overall picture is one of further genericization of the statin and Zetia market being more than compensated for by an increase in overall patient numbers and sales growth for the newer PCSK9 inhibitors as their profiles are backed up by solid cardiovascular outcomes (CVOT) data.

Specifically, Datamonitor Healthcare expects sales of Crestor/Zetia/Vytorin to decrease from $6.0bn in 2016 to $1.4bn in 2025. "The large dyslipidemia patient population and low switching costs associated with branded and generic oral therapies result in high rates of generic erosion."

All of the major statins have experienced patent expiry and subsequent erosion of sales due to strong generic competition. Crestor, the last major branded statin, lost market exclusivity in May 2016, and **Allergan PLC** has subsequently launched the first generic version of the drug, the analysts note. "Crestor is forecasted to follow in the footsteps of historical statin blockbuster, Lipitor, sales of which fell dramatically following the market entry of cheaper, generic equivalents."

Although statins will long continue to form the bedrock of dyslipidemia therapy, the market has in the meantime seen the arrival of the first products in the PCSK9 class, **Amgen Inc./Astellas Pharma Inc.**'s *Repatha* (evolocumab) and **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Praluent* (alirocumab). Behind them lie other investigational products, including inclisiran from **The Medicines Co.** and **Alnylam Pharmaceuticals Inc.** *(Also see "Medicines Company Gets Aggressive With Inclisiran Phase III Plans" - Scrip, 31 Aug, 2017.)*

Uptake of these new products has been stymied by strict reimbursement protocols of payers over the drugs' high yearly costs. "Both Praluent and Repatha have struggled to penetrate the US dyslipidemia market as a result of concerns over their high annual costs of around $14,000 (although discounts have been negotiated)," Datamonitor Healthcare noted.

Even so, the PCSK9 class is expected to achieve peak sales of $18.5bn by 2025, the analysts predict. "The high cost of PCSK9 inhibitors will help contribute to this revenue growth, and the PCSK9 inhibitors are being positioned as add-on therapies to statins, or as alternative therapies for statin-intolerant patients," the report says.

Key to their eventual success will be cardiovascular outcomes data and their role in securing their reimbursement. In March 2017, Amgen announced positive results from the FOURIER trial of Repatha, showing that the drug significantly reduced major cardiovascular events as compared to placebo.

"These positive findings are expected to help validate the high cost of this treatment and result in the easing of reimbursement restrictions by payers. Additionally, the strong clinical benefit shown in this trial is expected to further increase physician demand." The combination of easing of prior authorization restrictions and increase in physician demand is expected to result in strong uptake of the PCSK9 class, the analysts add.

In the longer term, the dyslipidemia market could be further bolstered by late-phase pipeline molecules, bempedoic acid (**Esperion Therapeutics Inc.**) as well as inclisiran, which are expected to provide physicians and patients additional options for lowering LDL-C levels.

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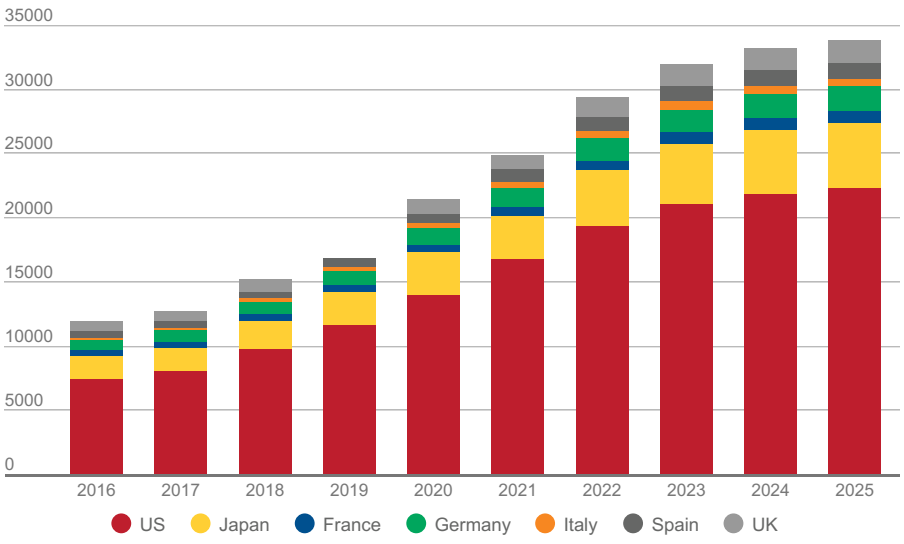
Dyslipidemia drug sales across the US, Japan, and 5EU, by country ($000), 2016–25



Source: Datamonitor Healthcare

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New Drugs Shine But Biosimilars Blunt Roche Revenue Rise

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Roche has coped well enough in the third quarter with the start of biosimilar competition to some of its big-selling therapies as new drugs contributed to better-than-expected sales but the signs are there that the threat will be considerable in the next year or so.

Group revenues rose 6% on the year-earlier period to CHF13.09bn at constant exchange rates, with pharmaceutical sales also up by 6% to CHF10.12bn. A healthy performance but alarm bells are ringing over a steeper-than-forecast decline in sales of *MabThera/Rituxan* (rituximab).

Roche is looking to soften the blow of biosimilars

It is still Roche's biggest earner, bringing in CHF1.78bn (+1%) but MabThera revenues sank 16% in Europe where the first biosimilars have been launched, namely **Sandoz Inc** 's *Rixathon* and **Celltrion Inc.** and **Mundipharma International Corp. Ltd.**'s *Truxima*. On a conference call, pharmaceuticals chief Dan O'Day said that market share erosion is progressing as Roche had expected and "we have no illusions that we can stop the decline."

However, he believes the company can still compete and show there is value in the originator product, as well as highlight the benefits of the subcutaneous version of MabThera. No other competitor is expected until 2019, O'Day confirmed, noting that the next-generation anti-CD20 antibody *Gazyva* (obinutuzumab) can help soften the biosimilar blow – sales of the latter in the first nine months were up 40% to CHF202m.

What will be equally damaging to Roche will be biosimilar competition to the HER2 breast cancer blockbuster *Herceptin* (trastuzumab). The first version, *Ontruzant* from **Samsung Bioepis Co. Ltd.**, was recommended for approval last month by European regulators and Roche is expecting several competitors from the beginning of 2018.

For the time-being though, the HER2 franchise of Herceptin, *Perjeta* (pertuzumab) and *Kadcyla* (ado-trastuzumab emtansine) is performing well with sales reaching CHF1.69bn (flat), CHF552m (up 17%) and CHF228m (up 10%), respectively. As for the multi-indicated cancer blockbuster *Avastin* (bevacizumab), third-quarter sales fell 4% to CHF1.59bn which O'Day said reflected a delisting for use in breast cancer in France and the rise of immunotherapy regimens for lung cancer.

On the bright side, a clear highlight in the quarter was the performance of *Ocrevus* (ocrelizumab) for the treatment of both the relapsing and primary progressive forms of multiple sclerosis. Sales hit a staggering CHF308m, way past analyst forecasts, and all that comes from the US as Roche is not going to get approval in Europe before the end of the year.

O'Day noted that 17,000 patients have been infused and the split is 60%/40% in favor of the relapsing form of the disease. Some 70% of patients have been switched from an even spread of other MS treatments on the market, he said, name-checking big-sellers such as **Biogen Inc.**'s *Tecfidera* (dimethyl fumerate) and *Tysabri* (natalizumab), **Teva Pharmaceutical Industries Ltd.**'s *Copaxone* (glatiramer acetate) and **Merck KGAA**'s *Rebif* (interferon beta-1a).

When asked why European regulators again delayed a decision on recommending approval of Ocrevus earlier this month, O'Day said it was not so surprising given that Roche has submitted "a very large file with huge amounts of datapoints". He expects a positive opinion for the drug by the end of the year but would not be drawn on pricing strategy, though pointed out that the price in the US (the wholesale acquisition cost was set at $65,000 on approval in the second quarter, lower than older therapies) was responsible in terms of safeguarding patient access and satisfying payors.

Much of the focus on Roche now involves the prospects for its PD-1/L1 inhibitor *Tecentriq* (atezolizumab). Sales of the immunotherapy doubled to CHF118m from the year-ago period but fell from the CHF124m posted in the previous quarter, due to a clinical setback in bladder cancer with the failure of a key trial and more difficult reimbursement conditions in the US.

Most of the questions on the conference call centered around the eagerly-awaited IMpower150 Phase III study examining the use of Tecentriq in combination with carboplatin and paclitaxel, with or without Avastin, in first-line non-squamous non-small cell lung cancer. O'Day confirmed that the study was still on target to read out between now and the end of the year, although the overall survival data may not be mature for another six months.

Some analysts have suggested that IMpower150 is crucial to Tecentriq's success and have been making less-than-positive noises about its possible outcome of late. O'Day said everyone would have to wait and see but also pointed to three other studies – IMpower130, 131 and 132 – which will read out next year and are exploring a variety of chemo and drug combinations with Tecentriq.

He concluded by saying that this is "wave two" for the immunotherapy which consists of adding Tecentriq to current standards of care, looking at different chemo backgrounds, use of steroids, and combinations with or without Avastin. "We've laid a lot of good scientific bets," O'Day claimed, and "the tremendous amounts of readouts" from Tecentriq trials coming up over the next year or so will help Roche find the best bet.

As for full-year forecasts, chief executive Severin Schwan said Roche was "cruising comfortably" meeting its previous sales guidance of mid-single digits growth at constant exchange rates, with core earnings growing broadly in line with sales. He noted that the MabThera biosimilar effect would become more pronounced in the fourth quarter but the new product uptake was encouraging.

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Lynparza Partners AZ And Merck & Co Target US Breast Cancer Market

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The three-month-old global collaboration between **AstraZeneca PLC** and **Merck & Co. Inc.** on jointly developing and commercializing AZ's anticancers, *Lynparza* (olaparib) and selumetinib, is getting closer to delivering on its promise, with the addition of a breast cancer indication for Lynparza in the US now expected in early 2018.

The multi-billion-dollar deal between the two big pharma companies is aimed at maximizing the use of the PARP inhibitor olaparib as the "preferred backbone" in several combination therapies for cancer, backed by the sales and marketing muscle of both companies, that in Merck & Co's case includes significant experience in the cancer field through its PD1-inhibitor *Keytruda* (pembrolizumab)

Now, the development and commercialization strategy for olaparib has just achieved a notable milestone. On Oct. 18, the two companies announced the product had become the first PARP inhibitor to have a regulatory submission for a non-ovarian cancer indication accepted for review by the US FDA. The drug has been granted a priority review for use in certain patients with breast cancer, with a PDUFA date sometime in the "first quarter of 2018". A filing for EU approval is expected in 2018.

The US supplemental NDA, for use in patients with germline BRCA-mutated HER2-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic settings, will expand the potential market for olaparib - breast cancer is much more common than ovarian cancer. The companies note that one in eight women will be diagnosed with breast cancer in the US, that is around 250,000 women in 2017, and there is no cure for patients with metastatic breast cancer.

The submission is based on the results of the Phase III OlympiAD study, which found olaparib monotherapy had a positive effect on progression-free survival when compared with "physician's choice" chemotherapy (capecitabine, vinorelbine, eribulin), in 302 patients with HER2-negative metastatic breast cancer with germline BRCA1 or BRCA2 mutations, which are predicted or suspected to be deleterious.

Olaparib was associated with a median PFS of seven months, versus 4.2 months for chemotherapy, a 42% reduction in risk. The objective response rate was 60% with olaparib versus 29% with chemotherapy. The international trial was conducted in 19 countries across Europe, Asia, North America and South America, and the results presented at this year's ASCO meeting. *(Also see "AstraZeneca's OlympiAD Trial Kick-Starts PARP In Breast Cancer" - Scrip, 5 Jun, 2017.)*

There is increasing evidence that PARP inhibitors and MEK inhibitors like selumetinib can be combined with other potential new medicines, as well as being developed as monotherapies, and AstraZeneca and Merck have agreed to collaborate on that work. However, the two companies will independently develop olaparib and selumetinib use in combination with their own PDL-1/PD-1 checkpoint inhibitors, that is Merck & Co with its PD-1 inhibitor Keytruda, and AstraZeneca with its PD-L1 inhibitor *Imfinzi* (durvalumab).

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'Lynparza will face increasing competition from recently approved PARP inhibitors'

The just-filed US supplemental NDA involves Lynparza 100mg and 150 mg tablets, a relatively new and more convenient formulation for patients that can be given as two tablets twice daily compared with the former hard capsule formulation given as eight capsules twice daily. The new tablet formulation was approved by the US FDA in August 2017 in expanded ovarian cancer indications - patients with platinum-sensitive recurrent disease regardless of BRCA status, and in those with BRCA-mutated disease beyond the third-line setting. *(Also see "Lynparza Poised For Growth With Broad Ovarian Cancer Approval" - Scrip, 17 Aug, 2017.)*

Accelerating the development of Lynparza in new indications is important because of the competitive nature of the PARP inhibitor sector. "Lynparza will face increasing competition from recently approved PARP inhibitors, **Clovis Oncology Inc.**'s *Rubraca* (rucaparib) and **Tesaro Inc./Takeda Pharmaceutical Co. Ltd.**'s *Zejula* (niraparib), as well as **AbbVie Inc.**'s late-phase competitor, veliparib," said analysts at Datamonitor Healthcare in a recent report. They expect Lynparza also to be filed for the first-line maintenance treatment of BRACA-mutated ovarian cancer in 2018, based on the results of the SOLO-1 trial.

The market for ovarian cancer drug sales is expected to increase from around $500m in 2016 to almost $2.7bn in 2025, driven by the PARP inhibitors and other anticancers in the late-phase R&D pipeline, and some commentators reckon the market opportunity for PARP inhibitors could be greater than $5bn. *(Also see "PARP Inhibitors: Rich Prospects And More Deals In Store?" - Scrip, 4 Sep, 2017.)*

Olaparib is not the only PARP inhibitor to attract a collaboration partner – Clovis has signed a non-exclusive agreement with **Bristol-Myers Squibb Co.** to test rucaparib with BMS's *Opdivo* (nivolumab) in ovarian, breast and prostate cancer. *(Also see "The PARP Combo Race Is On: Clovis And Bristol Partner On Rubraca" - Scrip, 31 Jul, 2017.)*

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Scrip Awards Finalists 2017

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Executive of the Year (sponsored by Lachman Consultants)

Private companies and those with a market cap of <$1bn

This award is designed to acknowledge excellence in the leadership of small or private pharmaceutical and biotechnology companies.

Eliot Forster, CEO of Immunocore

Eliot Forster has overseen a key period in Immunocore's growth, including a significant financial valuation uplift and major progress with its pipeline. He has begun to build Immunocore's presence, both geographically, through the opening of a US office, and scientifically, into adjacent therapy areas, all while holding the chairmanship of the industry body MedCity.

Kurt Graves, chair, president and CEO of Intarcia Therapeutics

Under Kurt Grave's leadership, Intarcia had a watershed year. It successfully launched the new Medici Drug Delivery System, raised more than $475m in private funding, including a partnership with The Bill & Melinda Gates Foundation, submitted its first NDA for its type 2 diabetes therapy, ITCA 650, and established a new partnership with California Institute for Biomedical Research.

Elizabeth Iorns, CEO and co-founder of Science Exchange

Elizabeth Iorns is co-founder and CEO of Science Exchange, the online marketplace for scientific research. Her vision is to enable breakthrough scientific discoveries by providing researchers with easy access to the world's best experimental service providers. She is also an active angel investor and a part-time partner at Y Combinator, a seed-stage accelerator.

Kevin Lee, CEO of Bicycle Therapeutics

During the qualifying 12 months, Kevin Lee transformed Bicycle Therapeutics' vision and strategy. He brought in a new and highly experienced management team, launched Bicycle's US subsidiary and led the company through multiple transformational milestones, including signing two important deals, with Cancer Research UK and a potential $1bn deal with AstraZeneca.

Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals

As president and CEO of Braeburn Pharmaceuticals, Behshad Sheldon redefined what it means to be a leader in the pharmaceutical industry. She led Braeburn as it made history with the approval of Probuphine, the first and only six-month implant treatment for opioid addiction, which was made available just 17 days after FDA approval.

Raman Singh, CEO of Mundipharma, Singapore

Raman Singh identifies the two most important elements of his job as people and patients. In spearheading extraordinary growth, he has created a corporate culture focused on patient-centricity, innovation and entrepreneurship. The example he sets has resulted in a highly motivated and engaged workforce that puts patients at the heart of everything they do.

Best Contract Research Organization – Specialist Providers

This award is to acknowledge the critical role that CROs which provide specialist services play in drug development.

Aptuit

Aptuit is a next-generation CRO, termed a PRO (Partnership Research Organization) that delivers outcome-based solutions for customers, from target validation to clinical POC and beyond. Aptuit is adept at combining its R&D knowledge with that of its customers to ensure that each drug candidate's potential is maximized whilst accelerating R&D time and reducing attrition.

Cytel

Cytel is the world's leading biometrics CRO which aims to maximize the value of clinical data and reduce customers' clinical development risks. Its key strengths include industry-leading experience in biostatistics, statistical programming and data management, expertise in adaptive trial designs, focus on innovation, and effective operational management.

Orphan Reach

Orphan Reach is the first CRO purely dedicated to rare diseases. Orphan Reach offers an extended feasibility study approach in over 50 emerging countries, using its relationships with therapeutic leaders and local patient advocacy groups to ensure that it can identify patients with a specific rare disease faster, and to reduce the risk of drop-outs.

Quanticate

Quanticate has become one of the world's largest CROs focused on the collection, analysis and reporting of clinical study data. Its niche clinical services include biostatistics, programming, data-management, medical writing and pharmacoviglance. Quanticate's sole focus on data services means that all of its effort and investment is targeted in this area.

PHASTAR

PHASTAR offers statistical consultancy and clinical trial reporting to pharmaceutical and biotech companies. It enjoyed 47% year-on-year growth from 2013 to 2015 and is on target to double in size by 2018. Its growth has been fuelled by continuing repeat business from satisfied customers, as well as business from new customers worldwide.

WuXi NextCODE

WuXi NextCODE is a contract genomics organization that is providing the global standard platform on which genomic and medical data are used, at scale to improve healthcare. The WuXi NextCODE platform powers the biggest and most innovative precision medicine efforts, including population-based target discovery, clinical interpretation and world-leading deep-learning capabilities.

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If Orexigen Disappears, Who's Left In The Obesity Market?

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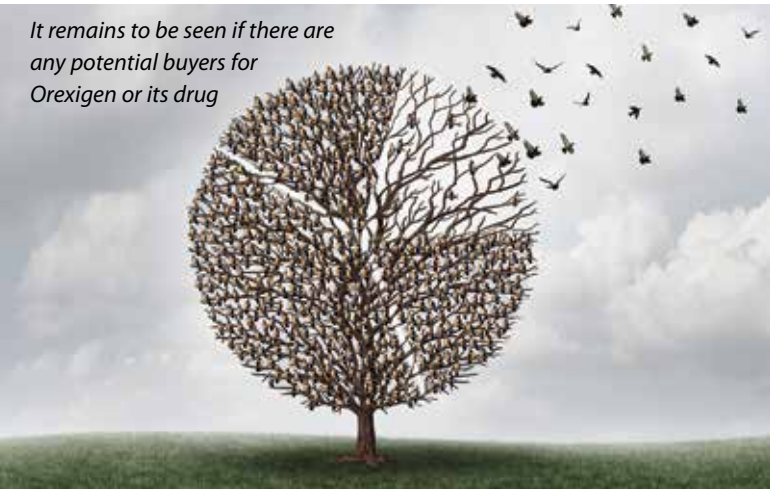

It remains to be seen if there are any potential buyers for Orexigen or its drug

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Orexigen Therapeutics Inc. had big plans for reinvigorating its weight-loss drug *Contrave* (naltrexone and buproprion), but now the company is worried about its ability to stay in business beyond next year, which could provide an opportunity for other players in the obesity market to grab market share.

San Diego-based Orexigen's aggressive marketing campaign since it regained full rights to Contrave last year pushed sales higher during the first half of 2017, but it appears that revenue slid lower in the third quarter, raising internal doubts about the company's ability to continue as a going concern. Obesity drugs from **Vivus Inc.** and **Arena Pharmaceuticals Inc.** also have struggled to gain traction in a market with hundreds of millions of patients, but **Novo Nordisk AS** so far has been able to capture significant and rising sales for *Saxenda* (liraglutide) in obesity – a franchise it hopes to expand with semaglutide.

Orexigen said in an Oct. 17 US Securities and Exchange Commission (SEC) filing that Contrave sales for the third quarter suggest an inability to meet the terms of notes due in 2020, which means the company may have to repay the debt two years early. Without enough cash on hand to keep selling Contrave and meet its potential near-term debt obligation, Orexigen is evaluating its ability to raise money, renegotiate its debt or find a buyer for the company.

Investors sent Orexigen's stock 3.3% higher to close at $1.89 on Oct. 17 following the preliminary look at third quarter performance and the disclosure of financial trouble ahead. The response to the company's update signaled that a sale of Orexigen or its assets may be viewed as the best way to generate value for shareholders. Notably, the company's stock price actually fell 3.9% a few days earlier on Oct. 13 when it reported good news – that Orexigen won its patent litigation against generic drug maker **Actavis Laboratories FL Inc.**, owned by **Teva Pharmaceuticals Industries Ltd**. The ruling maintains patent exclusivity for Contrave through 2030.

Orexigen said in its Oct. 17 SEC filing that it expects US Contrave sales to total $17m to $18m for the third quarter, although the accounting for July-to-September financial performance is ongoing. That estimate represents a quarter-over-quarter drop after Contrave generated $20.7m in US sales during the second quarter, which was a 69% year-over-year increase and an all-time quarterly high. First quarter sales totaled $14.8m in the US.

At that rate, US sales so far this year totaled about $53.5m, which means Orexigen will have to almost double that number in the fourth quarter to meet the terms of its convertible senior secured notes due in 2020. Note holders can redeem the notes after June 30, 2018, if net product sales in the 2017 fiscal year total less than $100m.

Unfortunately for Orexigen, adding in Contrave sales to ex-US partners isn't likely to bring in enough revenue to help the company meet the requirement of $100m in 2017 sales. Revenue from Contrave purchased for ex-US sales was nominal during the first half of this year – $4.3m in the first quarter and $2.7m in the second quarter.

The company estimates its cash and investments at $70.6m as of Sept. 30, which is less than its obligation related to the outstanding convertible debt, which had a fair value of $146.5m as of June 30 versus $101.9m at the end of 2016, due to the declining value of Orexigen's stock.

IF OREXIGEN FAILS, THEN WHAT?

It remains to be seen if there are any potential buyers for Orexigen or its drug, given Contrave's rocky performance and the poor sales history for Vivus' *Qsymia* (phentermine and topiramate) and Arena's *Belviq* (lorcaserin), the latter of which is marketed by **Eisai Co. Ltd.**

Vivus has reported mostly declining sales for Qsymia, dropping from $54.6m in 2015 to $48.5m in 2016. This year started off on a positive note with first quarter Qsymia sales of $17.6m versus $12.4m during the first three months of last year, but fell to $8.5m in the second quarter from $12.7m for the same period in 2016.

Meanwhile, Eisai has slowly de-prioritized commercialization of Belviq in its various markets. *(Also see "Obesity Market Snapshot: Marketing Partners Giving Obesity The Slow Goodbye" - Scrip, 9 May, 2016.)* Arena has moved on as well, focusing on non-obesity assets in its mid-stage pipeline. *(Also see "Beyond Belviq: Reinventing Arena To Focus On Phase II Candidates" - Scrip, 7 Feb, 2017.)* The company reported just $2.1m in net product sales for Belviq in the second quarter plus $1.8m in manufacturing support payments from Eisai.

However, Arena had $130.8m in cash as of June 30 plus $162m in proceeds from a stock offering initiated in July after the company reported positive Phase II results for ralinepag in peripheral arterial hypertension. *(Also see "Arena Rises, But Raises Questions With Phase II Ralinepag Data In PAH" - Scrip, 11 Jul, 2017.)*

Vivus also appears to be in a better financial position than Orexigen with $251.5m in cash at the end of the second quarter. The company ended its own patent litigation with Actavis in July, reaching a settlement that protects Qsymia's market exclusivity into 2024.

Regardless of the patent life left for Qsymia and Contrave, big pharma and smaller companies that are developing obesity drugs

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> Saxenda sales in the second quarter of this year totaled $109m – more than a full year of Contrave or Qsymia

may have a hard time justifying an investment in Orexigen's product, which pairs two drugs long available as generics to control appetite and cravings, and its competitors' floundering therapies.

NOVO'S SEMAGLUTIDE MAY BE NEXT APPROVAL

Diabetes specialists, like Novo, are especially focused on mechanisms that lower blood glucose and result in weight loss for diabetic patients.

Novo's Saxenda is a higher-dose formulation of Novo's blockbuster glucagon-like peptide-1 (GLP-1) receptor agonist *Victoza* that was approved in December 2014 as a once-weekly injection on top of dietary changes and exercise for obese patients and for overweight patients with at least one co-morbidity, such as hypertension, type 2 diabetes or high cholesterol. *(Also see "Novo's Saxenda bags FDA approval for weight management" - Scrip, 24 Dec, 2014.)* Contrave was approved with a similar label three months earlier. *(Also see "Contrave OK'd in obesity; multiple trials required" - Scrip, 11 Sep, 2014.)*

Saxenda sales in the second quarter of this year totaled $109m – more than a full year of Contrave or Qsymia – which was an 8% increase from the same period in 2016. However, Novo is focused on expanding its obesity market share via the next-generation GLP-1 receptor agonist semaglutide. *(Also see "Novo Nordisk: Semaglutide Heralds Commercial Dawn Of Obesity Market" - Scrip, 9 Aug, 2017.)*

The company will move semaglutide into Phase III next year after the drug provided weight loss of as much as 13.8% in patients treated for a year in a Phase II study, which compared favorably to the 5% placebo-adjusted weight loss seen for some of the more recently approved obesity drugs. *(Also see "Novo Nordisk's Great Hope Semaglutide Shines In Ph II Obesity Study" - Scrip, 26 Jun, 2017.)*

Like Saxenda, semaglutide is an injection, but an oral version also is in development. The once-weekly injectable has been submitted for FDA approval in the treatment of diabetes and so far has had a positive review from the agency. *(Also see "Smooth AdCom Passage Expected For Novo's Semaglutide Despite Retinopathy Queries" - Scrip, 17 Oct, 2017.)*

Semaglutide is one of the most advanced weight-loss therapies in the biopharmaceutical industry's research and development pipeline, but it's at least a few years from approval. That will give Saxenda, Contrave, Qsymia, Belviq and **Roche's** reversible inhibitor of gastrointestinal lipases *Xenical* (orlistat) a few more years to keep trying to expand the obesity market.

Biomedtracker's database and clinicaltrials.gov show that there are seven active mid-stage drug development programs in the pipeline for various obesity indications (*see table below*). Biomedtracker also lists 20 Phase I candidates, seven investigator-initiated programs and 14 preclinical assets.

These programs and recent deal-making reflect the attraction of the obesity market, which has hundreds of millions of patients worldwide. Datamonitor Healthcare determined in its December 2016 report that the obesity market could grow from $533m to $1.2bn in 10 years, but it would generate as much as $11.2bn in biopharma sales in 2026 if companies were able to capture just 5% of the market. *(Also see "Obesity Market Gains Weight But Better Drugs Still Needed" - Scrip, 25 Nov, 2016.)*

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Active Phase II Obesity Drug Programs

COMPANY	DRUG	MECHANISM	STATUS
Rhythm Pharmaceuticals Inc.	Setmelanotide	Melanocortin 4 receptor (MC4R) agonist	A Phase III trial was announced in September, but had not started enrolling patients, in the ultra-orphan indication of early onset leptin receptor (LEPR) deficiency obesity due to bi-allelic loss-of-function LEPR genetic mutation.
Johnson & Johnson	Invokana (canagliflozin)	Sodium-glucose cotransporter-2 (SGLT2) inhibitor	Phase II results for Invokana plus phentermine were reported in 2016. Mitsubishi Tanabe, which markets the drug for diabetes in Japan, still lists Invokana as being in Phase II for obesity.
Novartis AG	LIK066	SGLT1/2 inhibitor	Phase II trials were initiated or announced this year to study LIK066 in obese or overweight patients for 24 weeks and in obese patients with non-alcoholic steatohepatitis (NASH) for 12 weeks.
Raziel Therapeutics Inc.	RZL-012	A novel small molecule injected directly into subcutaneous fat	A placebo-controlled Phase IIa dose escalation study is under way in obese and overweight volunteers.
Hanmi Pharmaceutical Co. Ltd. and Sanofi	SAR439977 (efpeglenatide)	GLP-1 receptor agonist	Phase IIb results in obese diabetes patients were reported in 2015 and viewed as positive, but comparable to Saxenda. Hanmi still lists the drug in Phase II for diabetes and obesity.
Novo Nordisk	Semaglutide	GLP-1 receptor agonist	Entering Phase III next year for obesity; US approval pending in diabetes.
Saniona AB	Tesofensine	Inhibits re-uptake of dopamine, noradrenaline (norepinephrine) and serotonin	Development previously was suspended in diabetes as well as in Alzheimer's and Parkinson's diseases. Partner Medix initiated a Phase III obesity study this year in Mexico.

Novo's Semaglutide: Retinopathy Warning Unlikely To Dim Commercial Prospects

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A US FDA panel's recommendation for a retinopathy label warning on **Novo Nordisk AS**' semaglutide seems unlikely to dim the GLP-1 receptor agonist's commercial prospects given its robust glycemic control effects and reassuring cardiovascular safety profile.

At an Oct. 18 meeting, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 16-0, with one abstention, that the efficacy and safety data support approval of once-weekly semaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Panelists pointed to impressive and sustained reductions in hemoglobin A1c in the semaglutide clinical program, which included placebo- and active-controlled trials.

They also remarked upon the drug's weight-reduction effects and were reassured by results from the SUSTAIN-6 cardiovascular outcomes trial (CVOT), which not only showed a benign CV safety profile but a statistically significant, 26% reduced risk of major adverse cardiovascular events.

LABEL WARNING AND POSTMARKETING STUDY ANTICIPATED

The approval recommendation followed a lengthy discussion about an increase in diabetic retinopathy complications among semaglutide-treated patients in SUSTAIN-6. Committee members generally agreed the retinopathy risk was clinically manageable and could be addressed through a label warning. Novo has proposed a retinopathy warning in labeling, but not a boxed warning or Risk Evaluation and Mitigation Strategy.

"The panelists concluded that the benefits of semaglutide outweighed the safety risks, which suggests a clear path to timely approval with standard warning language highlighting the risk of retinopathy associated with intensive glucose-lowering therapy," Leerink's Seamus Fernandez said in an Oct. 18 note.

"The increased risk of retinopathy is expected to be reflected in the warning section of the label, especially for those having retinopathy at baseline, but no more (no black box in particular)," Bryan, Garnier & Co. analyst Eric Le Berrigaud said in an Oct. 19 note.

Committee members said a study to further assess the drug's retinal effects in the long term would be "desirable" but should not be required prior to approval.

Berrigaud noted that when the FDA approved **Sanofi**'s *Lantus* (insulin glargine) in 2000, it requested a five-year, 1,000-patient study to assess retinopathy risk. "We might expect something similar to happen with semaglutide," he said.

Some advisory committee members also suggested the retinopathy study could be embedded within a larger, longer CVOT conducted after approval to support a possible CV benefit claim. SUSTAIN-6 was powered for noninferiority on safety, not superiority on benefit. Novo has said it expects to conduct another CVOT after approval but has not provided any details. *(Also see "EASD 2016: Semaglutide Steals The Show With Impressive Cardiovascular Outcomes Data" - Scrip, 16 Sep, 2016.)*

Novo Nordisk told Scrip that the SUSTAIN-6 data provide "important insights into the potential CV safety of semaglutide. At this time, we are in discussions with the FDA about inclusion of these data in the prescribing information and can't comment any further as the application is still under review."

NOVO BANKING ON SEMAGLUTIDE

Semaglutide is a long-acting, follow-on to Novo's blockbuster, once-daily GLP-1 agonist *Victoza* (liraglutide).

With a user fee goal date in December, semaglutide is on track to join a group of once-weekly GLP-1 agonists that includes **AstraZeneca PLC**'s *Bydureon* (exenatide extended-release), **Eli Lilly & Co.**'s *Trulicity* (dulaglutide) and **GlaxoSmithKline PLC's** *Tanzeum* (albiglutide). *(Also see "Smooth AdCom Passage Expected For Novo's Semaglutide Despite Retinopathy Queries" - Scrip, 17 Oct, 2017.)*

GSK has announced plans to discontinue manufacturing and sale of albiglutide by July 2018 due to market penetration challenges, a steady decline in sales and availability of multiple treatment options. *(Also see "Walmsley Shakes Up GSK; Cuts More Than 30 Drug Development Programs" - Scrip, 26 Jul, 2017.)*

Novo has seen liraglutide's US market share slip as a result of pricing pressures and competition from once-weekly products. However, it has high commercial expectations for semaglutide, which is also being studied in obesity and has an oral formulation under development. *(Also see "Semaglutide Should Transform Novo Nordisk's Prospects, CSO Says" - Scrip, 31 May, 2017.)*

In August, Novo announced that semaglutide outperformed dulaglutide, the current once-weekly GLP-1 market leader, on glycemic control and weight loss in the SUSTAIN-7 study. *(Also see "Novo's Semaglutide Outperforms Lilly's Trulicity In SUSTAIN 7" - Scrip, 16 Aug, 2017.)*

Datamonitor Healthcare is forecasting semaglutide will become the market leading injectable GLP-1 agonist with peak revenue of $2.5bn, though revenue will be limited somewhat by oral semaglutide and generic or biosimilar versions of liraglutide.

LARGE DECLINES IN HBA1C LEVELS

There was little controversy about semaglutide's efficacy in either FDA's briefing document or the panel discussion at the advisory committee meeting. The NDA is supported by five key efficacy Phase III trials (two placebo-controlled and three active-controlled) and the SUSTAIN-6 CVOT.

In the placebo-controlled efficacy trials, semaglutide produced mean reductions from baseline HbA1c ranging from 1.3% to 1.7% at 30 weeks, the FDA's clinical reviewer Andreea Lungu said. Mean reductions from baseline body weight compared to placebo ranged from 2.2 kg to 4.7 kg at 30 weeks.

In the two-year SUSTAIN-6 trial, HbA1c was reduced by 0.66% and 1.05% with semaglutide 0.5 mg and 1 mg, respectively, compared to placebo, FDA reviewers said, noting this difference is larger than has

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been seen in previous CVOTs of antidiabetic drugs.

In the active-controlled trials, both semaglutide doses (0.5 mg and 1.0 mg) demonstrated superiority to **Merck & Co. Inc.**'s DPP-4 inhibitor *Januvia* (sitagliptin) and insulin glargine on HbA1c reduction, and semaglutide 1.0 mg was superior to exenatide extended-release.

Save for the retinopathy findings, semaglutide's safety was generally consistent with other GLP-1 agonists, with gastrointestinal events the most commonly reported adverse events and a low inherent risk of hypoglycemia, Lungu said.

Advisory committee members were clearly moved by semaglutide's ability to reduce HbA1c levels.

> 'The risk factors and complications of retinopathy are well recognized. The retinopathy complications discussed can be effectively monitored, managed and treated by adhering to current clinical practice guidelines'

"I was impressed by the efficacy results in terms of how robust the A1c lowing was in the setting of a low risk of hypoglycemia," said Melissa Li-Ng, a Cleveland Clinic endocrinologist. "I was also impressed by the sustainability of the A1c lowering even at 104 weeks. We don't see that sustainability with some of the oral agents, such as the DPP-4 inhibitors."

Cecilia Low Wang, associate professor of medicine at the University of Colorado, said, "It was great to see this degree of A1c lowering, especially compared to another GLP-1 receptor agonist and some of the other agents that are available."

And Susan Yanovski, co-director of the Office of Obesity Research at the National Institute of Diabetes and Digestive and Kidney Diseases, said, "It was an impressive degree of A1c lowering but this was also in the context of, I think, an impressive amount of weight loss," said

WORSENING RETINOPATHY

Semaglutide's significant effects on glycemic control underpinned Novo's theory on why there was a higher rate of diabetic retinopathy complications with semaglutide in SUSTAIN-6. Fifty patients in the semaglutide arm and 29 in the placebo group experienced diabetic retinopathy complications, resulting in an estimated hazard ratio of 1.76 (95% CI: 1.11, 2.78).

Diabetic retinopathy complications were more likely to occur in patients who were younger, had longer duration of diabetes, had higher baseline HbA1c and were on insulin treatment. Approximately 84% of the subjects who experienced diabetic retinopathy complications had retinopathy at baseline compared to 29.4% in the overall population, the FDA said.

Novo attributed the imbalance in diabetic retinopathy complications to the CVOT's high-risk population, its decision to purposely look for retinopathy adverse events in the trial, and large HbA1c decreases produced by semaglutide relative to placebo.

The company asserted the increase in complications is consistent with early worsening of pre-existing diabetic retinopathy after improvements in glycemic control seen with other highly efficacious blood glucose-lowering therapies, including insulin in the Diabetic Control and Complications Trial. DCCT and other studies have shown long-term benefits on retinopathy with intensive glycemic control despite this early worsening of the condition.

Semaglutide's effect on glycemic control was greater than expected in SUSTAIN-6 and, consequently, Novo did not anticipate the retinopathy findings, said Stephen Gough, senior principal clinical scientist at the company.

"Because we did observe early worsening, the proposed label for semaglutide would include language about diabetic retinopathy that parallels labeling for insulin," Gough said. "This will include reference to the well-established guidelines and protocol for the management of patients at risk for early worsening."

A COMMON BUT MANAGEABLE CONDITION

Novo consultant Lloyd Paul Aiello, professor and vice chair of the department of ophthalmology at Harvard, described diabetic retinopathy as one of the most prevalent microvascular complications with diabetes, albeit one that is easily identified and readily managed.

At the time of diagnosis with type 2 diabetes, approximately 20% of patients have retinopathy. This incidence increases to more than half of all patients after 15 or more years with the disease, at which point approximately one-quarter of patients have advanced sight-threatening disease, Aiello said.

Under current American Diabetes Association clinical guidelines, diabetics with no retinopathy or only mild disease should be seen by an ophthalmologist every one or two years, and frequency of monitoring increases with level of retinopathy. Patients with severe, nonproliferative retinopathy who initiate insulin should be seen every three months for six to 12 months, Aiello said.

"The risk factors and complications of retinopathy are well recognized. The retinopathy complications discussed can be effectively monitored, managed and treated by adhering to current clinical practice guidelines," Aiello said. "We currently have highly effective interventions for treating complications of diabetic retinopathy, and multiple studies conclusively demonstrate that better glycemic control is associated with reduced risk of retinopathy progression and visual loss."

LITTLE DISCOMFORT ABOUT RISK

Panelists generally agreed with Novo's proposal for a label warning similar to language that appears in the Adverse Reactions section of insulin labeling about transitory worsening of retinopathy with insulin initiation and intensification of glucose control.

"I don't know if there's an adverse retinopathy effect or not, but it seems prudent if somebody's going to suddenly improve their blood glucose that they get regular eye exams, so I'm not worried about that," said Frederick Ferris, director of the Division of Epidemiology and Clinical Applications at the National Eye Institute.

"Retinopathy is, in my view, a modest concern that is outweighed by the benefit otherwise seen," said Paul Palevsky, chief of the renal section of VA Pittsburgh Healthcare System. "I support the sponsor's proposal for labeling similar to that for insulin in terms of the risk of retinopathy progression.

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Brexit Ambiguity A Top Priority For Bayer's New UK & Ireland CEO

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Bayer AG's new CEO for the UK and Ireland, Lars Bruening, is preparing to manage the business in uncertain times as Brexit proceedings play out; using his market access background as an advantage he also plans to continue "strong" discussions between pharma and healthcare systems with the aim of improving uptake of new drugs in the UK & Ireland.

Previously based in Berlin as head of market access for Bayer, Bruening replaces Alexander Moscho as the chief of the German big pharma's operations in the UK and Ireland. Moscho left the company in August this year and is now head of corporate strategy and business development at **UCB Group**; he is also a member of the Belgium-based company's executive committee.

Bruening, who previously held senior commercial roles within Bayer in Europe, the Middle East and Asia, told *Scrip* in an exclusive interview that Brexit and slow uptake of innovative medicines were the biggest challenges facing the pharma industry in the UK.

"In the pharma business, we look at how we can constantly grow our contribution to medicine for UK patients and all parts of society. Keeping this in mind, Brexit is one of the element that we must manage over the coming years," he said.

BREXIT ISSUES – ONE IN ONE OUT

As the head of the UK and Ireland, Bruening has the complex job of managing one region firmly in the Europe Union and one that is on its way out of the EU. "Recently, I was asked internally about how management of Ireland and the UK might change after Brexit, and I said very honestly to my colleagues that I do not know at this stage. We need to know what Brexit will truly look like to know whether it is right to manage the UK and Ireland together or if we need to separate the regions. In this phase, I think it is great to manage both territories together."

Bruening said Brexit uncertainty was creating two key problems for Bayer. Firstly, the confusion around Brexit creates work because the company needs to prepare for several sets of circumstances. "Preparing for Brexit scenarios creates a complex setup to manage and it takes extra effort, some of which will be not be needed in the longer-term… this is not a nice situation to have," he said.

Lars Bruening, CEO of Bayer UK & Ireland

'We are not a closed shop; we engage with the healthcare systems in the UK and Ireland and we engage with other industries'

Secondly, Brexit uncertainty has caused companies to hesitate with decision-making. As an example, Bruening highlighted that while the UK was a strong company for clinical development, groups running clinical trials have asked if it still the best situation to include the UK in programs. "These questions happen and so far, we are able to say 'don't worry'. However, we need to get out of this uncertainty phase to avoid long-term impact," he said.

After Brexit, Bruening is not overly concerned about disruption to drug regulatory procedure in the UK. "From a regulatory standpoint, the MHRA is an impressive body that has played a key part in European Medicines Agency's processes. There will continue to be close collaboration between these groups that will benefit both the EU and the UK," he said. However, he said greater clarity would be critical to avoiding any regulatory disruptions or delays on new products reaching patients. The MHRA (Medicines and Healthcare products Regulatory Agency) is the UK's drug and device regulator, part of the Department of Health.

"The UK has an inherent strength for life sciences that has worked well in the current environment and it will remain strong as the landscape changes," Bruening said, adding that the region had solid R&D foundations in areas like oncology, cardiovascular disease and gene therapy, amongst others.

COLLABORATING WITH HEALTHCARE SYSTEMS

As well as bringing new drugs to market, Bruening said Bayer had an important element of being a company within society. "We are not a closed shop; we engage with the healthcare systems in the UK and Ireland and we engage with other industries."

He believes Bayer is acting as an "industry-leader" in the way it works with healthcare systems like the NHS (National health Service). Fostering the right dialog between key stakeholders in the healthcare paradigm has been vital to improving the uptake of new medicines, he said.

"Even when we get NICE approval, uptake in the UK is not the fastest," he noted. "We are working a lot with the NHS on the best ways to improve uptake of new products. This kind of collaboration is win-win because the use of new products that are meaningful for patients is an achievement for the system and for our company. The leading aspect for us is always the impact of our drugs on patients."

He added that Bayer had been working closely with physicians, pharmacists and nurses to improve uptake of novel products. "We have a very good dialog for how we can enhance treatment for patients. Our dialog with these partners is not spe-

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cific to a medicine; it's focused on the delivery of care to patients. This is the right conversation to have."

AN OPEN COMPANY

In terms of working more broadly within society, Bruening also highlighted Bayer's BayLab initiative. Based within the company's UK headquarters in Reading, BayLab is fitted with state of the art equipment and can demonstrate to visiting children scientific experiments from the national curriculum that not every school has the equipment to do.

"We have gotten feedback from pupils that for the first time they have found science interesting and fascinating, and it has changed maybe the way they had been looking at their futures," he said. "This is great because we need these kids, we need them to develop new ideas for science, have a good understanding of science and even follow a career in science."

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Silence Seeks Share Of Alnylam RNAi Success In Legal Action

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As **Alnylam Pharmaceuticals Inc.** finalizes plans to file the first RNA interference therapeutic, patisiran, the UK's **Silence Therapeutics PLC** has begun the next phase of its legal moves to claim intellectual property rights and a share in any success of this and other drugs in this closely-watched field.

In July, Silence launched an action in the UK High Courts of Justice (Patents Court) against US-based Alnylam, its UK affiliate and The Medicines Company UK and this week has delivered to the defendants its claim for "declaratory relief" relating to its entitlement to supplementary protection certificates (SPCs) on certain Alnylam products. SPCs can extend a patent right for a maximum of five years.

Specifically, the claim asks the Court to determine whether Silence is entitled to SPCs on certain late-stage Alnylam assets, which include patisiran for hereditary ATTR amyloidosis, fitusiran for hemophilia, givosiran for acute hepatic porphyrias, cemdiran for atypical Hemolytic-Uremic Syndrome (aHUS) and inclisiran (which is partnered with The Medicines Company and is in trials for inclisiran for hypercholesterolaemia).

Silence's position is that it believes Alynam's RNAi candidates, and indeed other companies' assets, require licenses under its chemical modification patent portfolio. The company stressed that it was "committed to defending its intellectual property".

As for the timing of the legal action, Laura Roca-Alonso, head of corporate development at Silence, told *Scrip* that as patisiran and other competitor drugs move closer to filing, the structures of these products become more visible and can be reviewed for possible IP breaches.

The world of patents is notoriously complicated, but Roca-Alonso explained that simply put, the patent protection Silence has covers the unique structural features of its siRNA molecules. Without Silence's chemical modifications, the siRNA would be degraded as soon as you put it in the body and would become inactive.

The London-headquartered company's chemical modification technology helps make the molecules more stable, more potent and less immunogenic – they require lower doses and the effect lasts longer, all of which are crucial for RNAi therapies, she adds.

Roca-Alonso went on to say that the IP of Silence is "quite unique as we are one of the pioneers in this technology" and its first batch of patents date from 2003. However, those patents, which cover broad claims, will start to expire in 2023, which explains the desire to get the SPC five-year extension.

> Alnylam believes it has not infringed any valid patent claims and said it will vigorosly defend itself against any legal action by Silence

Silence believes it needed to act because Alnylam has not asked for a license. The firm does have a licensee for its AtuRNAi technology, **Quark Pharmaceuticals Inc.**, which uses the latter for **Novartis AG**-partnered QPI-1002 – the drug recently met its primary endpoint in a Phase II trial in patients with acute kidney injury.

Silence has announced another slew of patents that have just been granted in the US that cover its chemical modification technology but the Europe case is the most urgent. High Court claims such as this can take a year to decide upon, with a six-month appeal period if needed for dispute resolution.

The company clearly thinks it has a strong case and Roca-Alonso told *Scrip* that success in the courts would boost Silence's status with investors.

For its part, Alnylam believes it has not infringed any valid patent claims and said when the case was first brought that it will vigorosly defend itself against any legal action by Silence.

These are exciting times for Alnylam which announced positive Phase III data for **Sanofi**-partnered patisiran in September. CEO John Maraganore said during a call to unveil the APOLLO study's top-line results that "frankly, we could not have dreamed for a better outcome," a sentiment echoed by the markets, following the first ever positive Phase III results for an RNAi therapeutic.

Alnylam unveiled a potentially lucrative agreement with **Vir Biotechnology Inc.** (the recently-launched biotech led by ex-**Biogen Inc.** CEO George Scangos) to develop RNAi therapeutics for infectious diseases, expects to file patisiran in the US by the end of the year and in Europe in early 2018.

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

CLICK
Visit scrip.pharmamedtechbi.com for the entire pipeline with added commentary.

Selected clinical trial developments for the week 13-19 October, 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Celgene Corp.	mongersen	Crohn's disease	REVOLVE, SUSTAIN; after data review.
Phase III Results Published			
Pfizer Inc./Takeda Pharmaceutical Co. Ltd.	*Xeljanz* (tofacitinib)	psoriatic arthritis	OPAL BEYOND; *NEJM*, Oct. 19, 2017.
Alkermes PLC	*Vivitrol* (naltrexone) extended-release	substance use disorder	*JAMA Psychiatry*, Oct. 18, 2017.
Updated Phase III Results			
Ionis Pharmaceuticals Inc.	inotersen	hereditary TTR amyloidosis with polyneuropathy	NEURO-TTR; clinical benefit seen.
Fennec Pharmaceuticals Inc.	*Pedmark* (sodium thiosulfate)	cisplatin-induced hearing loss	SIOPEL 6; met primary endpoint.
Merck & Co. Inc.	*Keytruda* (pembrolizumab)	metastatic non-small cell lung cancer, first-line	KEYNOTE-024; overall survival improved in updated results.
Merck & Co. Inc.	Keytruda plus pemetrexed, carboplatin	NSCLC, first-line	KEYNOTE-021; overall survival continued to improve.
TiGenix NV/Takeda Pharmaceutical Co. Ltd.	Cx601	Crohn's disease, fistula	ADMIRE-CD; remission observed.
Ardelyx Inc.	tenapanor	irritable bowel syndrome with constipation	T3MPO; significant benefits in pain and stool frequency.
AstraZeneca PLC	*Imfinzi* (durvalumab)	NSCLC	PACIFIC; patient reported outcomes.
Agile Therapeutics Inc.	*Twirla* low-dose combination patch	contraception	SECURE; spotting rates declined over time.
TherapeuticsMD Inc.	TX-001HR	menopausal symptoms	REPLENISH; clinically meaningful improvement.
Phase III Interim/Top-line Results			
Exelixis Inc./Ipsen	cabozantinib	advanced liver cancer	CELESTIAL; improved overall survival.
Dermira Inc.	glycopyrronium tosylate, topical	primary axillary hyperhidrosis	ARIDO; long term extension, well tolerated.
Phase III Announced			
Boehringer Ingelheim GMBH	nintedanib	scleroderma	A long-term safety study.
GlaxoSmithKline PLC	*Benlysta* (belimumab) plus rituximab	systemic lupus erythematosus	BLISS-BELIEVE; in adult patients.
Novimmune SA	emapalumab	lymphohistiocytosis	In pediatric patients.
Clementia Pharmaceuticals Inc.	palovarotene	fibrodysplasia ossificans progressiva	MOVE; in 80 subjects.
Immune Design Corp.	CMB305, a cancer vaccine	synovial sarcoma	In a prime-boost approach.
BioMarin Pharmaceutical Inc.	BMN-270 gene therapy	haemophilia A	In severe disease.
Societa Industria Farmaceutica Italiana SPA	polyxamethylene biguanide	acanthamoeba keratitis	An ophthalmic solution.

Source: Biomedtracker

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UK R&D Centre for Antimicrobial Resistance Goes Into Battle

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The UK's R&D Centre for Antimicrobial Resistance announced its first two collaborations in September and will soon be inking two more. Established in May 2016 as part of the UK's response to the global threat from antimicrobial resistance, the AMR Centre is based at Alderley Park near Manchester, northern England, a joint private-public initiative to support and accelerate development of new antibiotics and diagnostics using an integrated development capability and offering translational R&D from preclinical hits through to clinical proof of concept.

The idea behind the AMRC was conceived during the tenure of former British Prime Minister David Cameron, a big supporter of finding ways to effectively combat antibiotic resistance. It was under his direction that former Goldman Sachs economist Jim O'Neill conducted in depth analyses of the AMR crisis and brought the issue to the collective attention of world leaders.

The AMRC's mission was to get new, novel and needed antimicrobial drugs and diagnostics to market in the shortest possible time, irrespective of cost and origin. But Britain's referendum decision in June 2016 to leave the EU - and subsequent changes in the UK government - forced the AMRC to rethink how it operates, Ian Grundy, chief business officer at AMRC told *Scrip*.

"We were initially encouraged to set up this organization by Cameron and [then chancellor of the exchequer George] Osborne and [former treasury minister Jim] O'Neill, but then the Brexit vote happened and the whole landscape changed – funding from central government initially earmarked to support the operation fell away, and that meant that we had to refocus and redesign the organization and effectively look for the supporting funds in different locations, primarily in Northern England, and that's what we did," Grundy said in an interview. *(Also see "Jim O'Neill Is "Free For Global AMR Role" After Leaving UK Government" - Pink Sheet, 23 Sep, 2016.)*

AMRC today is a limited corporate entity with a partnering model aimed at progressing research through to clinical trials quickly, so that treatments can be brought to market and the threat of antimicrobial resistance can be significantly reduced.

Antibiotic discovery is challenging because bacteria are able to genetically modify and become resistant to medicines. Big pharmaceutical companies have meanwhile heavily cut their investment in antibiotic research because it has not been sufficiently profitable.

Stepping into the breach, the AMR Centre today has around 20 chemists and microbiology scientists in its laboratories at Alderley Park working on new antibiotics.

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APPOINTMENTS

Five Prime Therapeutics Inc., a company focused on immuno-oncology therapeutics, has appointed its chief operating officer (COO) ***Aron Knickerbocker*** as CEO and president – effective Jan. 1, 2017. Knickerbocker will succeed Lewis T. Williams, the current president, CEO and chair of the board, who will continue as executive chair of the company's board. Knickerbocker joined the company in 2009 and before his position as COO, he was executive vice president and chief business officer.

Depomed Inc., a company focused on pain and neurology related disorders, has named ***Santosh J. Vetticaden*** senior vice president, chief medical and scientific officer. Vetticaden has more than 25 years of pharmaceutical and biotechnology industry leadership experience and most recently, he was interim CEO of **Insys Therapeutics Inc.** Previously, he was chief medical officer at **Mast Therapeutics Inc.**, **Cubist Pharmaceuticals Inc.** and **Maxygen Inc.**

Gilead Sciences Inc. has promoted ***Alessandro Riva*** to executive vice president, oncology therapeutics. Riva joined the company in January 2017 as senior vice president, hematology and oncology therapeutic area head. Before Gilead, Riva was head oncology development at **Novartis AG.**

Aelix Therapeutics Inc. has appointed ***Thomas Hecht*** chair of its board of directors. Hecht is chair of the supervisory board at **Affimed NV**, chair of the board at **Cell Medica Ltd.** and **Vaximm AG.** Previously he has worked at **Amgen Inc.** and is currently head of Hecht Healthcare Consulting in Küssnacht, Switzerland, a biopharma consulting company.

Robert Karr has joined Verseon's board of directors as non-executive director. Karr has been a member of the company's scientific advisory board and has held various senior management roles in the pharmaceutical and biotech industry. Previously, he was senior vice president of R&D strategy at **Pfizer Inc.**, president of **Idera Pharmaceuticals Inc.**, and vice president of R&D strategy for **Warner-Lambert Co**. and G. D. Searle.

Giles Kerr has joined **Arix Bioscience** as non-executive director and chair of the board's audit committee – effective immediately. Kerr is the director of finance at the University of Oxford and carries 36 years of finance experience, with a focus on life sciences. He is also a director of Oxford University Innovation Ltd., **Adaptimmune Therapeutics PLC.**, **BTG PLC.**, Senior Plc. and PayPoint Plc. Previously, Kerr was chief financial officer of Amersham Plc., which was acquired by **GE Healthcare** in 2004.

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