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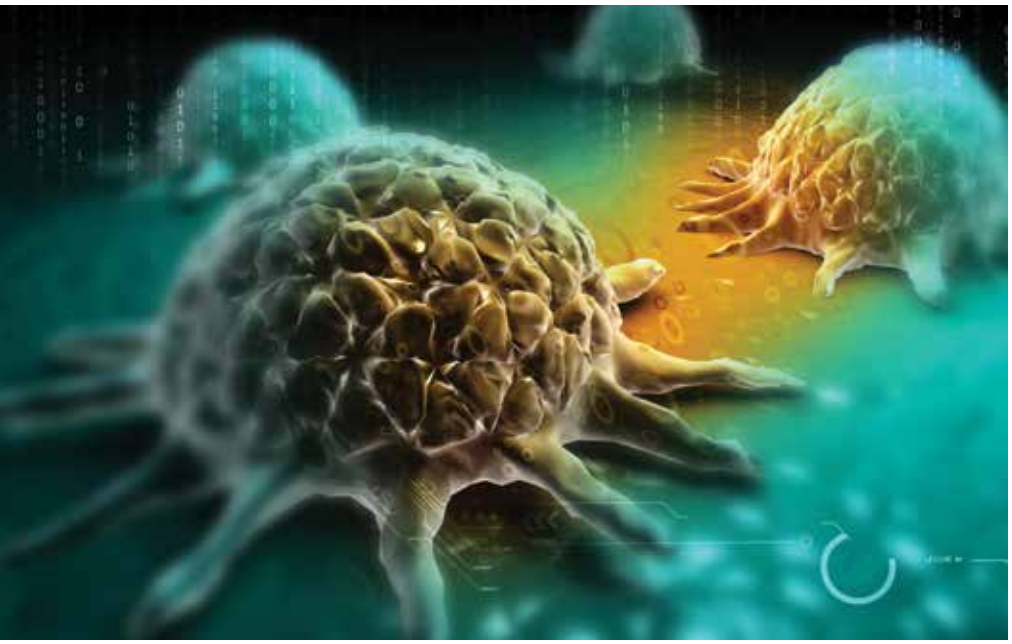

Pfizer's Three-Pronged Oncology Strategy

BRENDA SANDBURG brenda.sandburg@informa.com

As **Pfizer Inc.** continues to grow its oncology business, it's pushing both new molecules and expanding the indications of its approved drugs.

Andy Schmeltz, global president of Pfizer Oncology, described the company's strategy as a three-pronged approach at a May 15 press briefing at Pfizer's New York headquarters ahead of the American Society of Clinical Oncology (ASCO) annual meeting June 1-5 in Chicago.

The first prong of Pfizer's strategy is to build on anchor treatments for breast and prostate cancer. The company is looking to extend the indications for *Ibrance* (palbociclib), a CDK4/6 inhibitor approved for metastatic breast cancer, and *Xtandi* (enzalutamide), approved for metastatic castration-resistant prostate cancer, for use in earlier non-metastatic cancer.

A supplemental application for the expanded Xtandi indication is pending at the FDA with a user fee date in July after the company released positive Phase III data from the PROSPER trial last year, which showed improvement in metastasis-free survival in patients with non-metastatic, castration-resistant prostate cancer. The company also has a PARP inhibitor, talazoparib, in development for breast and prostate cancer. *(Also see "Pfizer Poised To PROSPER From Xtandi In Expanded Indication" - Scrip, 14 Sep, 2017.)*

Schmeltz said the second prong is to deliver precision medicines in lung cancer and hematologic malignancies.

The company is developing a follow-on to *Xalkori* (crizotinib), its first-in-class anaplastic lymphoma kinase (ALK) inhibitor, in lung cancer. The new compound, lorlatinib, was developed to address people who have developed resistance to ALK inhibitors. It received priority review as a second-line treatment for patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) and has a user fee date in August.

Pfizer also filed an NDA for dacomitinib, a pan-human epidermal growth factor receptor (EFGR) tyrosine kinase inhibitor for first-line treatment of locally advanced or metastatic NSCLC. It received a breakthrough therapy designation and priority review and has a user fee date in September.

Pfizer will present overall survival results from a study of dacomitinib versus **AstraZeneca PLC**'s *Iressa* (gefitinib) at ASCO. The company also will present Phase II results for Ibrance in combination with **Eli Lilly & Co.**'s *Erbitux* (cetuximab) in platinum-resistant human papillomavirus (HPV)-negative recurrent/metastatic head and neck squamous cell carcinoma.

In hematology, Schmeltz said the company has quietly built a presence with *Bosulif* (bosutinib), approved for Philadelphia chromosome-positive chronic myelogenous leukemia. Last year, FDA approved *Besponsa* (inotuzumab ozogamicin) for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). And the agency okayed the return to market of the acute myeloid leukemia (AML) treatment *Mylotarg* (gemtuzumab ozogamicin), which had been withdrawn in 2010.

CONTINUED ON PAGE 8

from the editor

eleanor.malone@informa.com

With ASCO starting today, we report inside on companies that have got ahead with cancer updates in advance of the Chicago conclave. Pfizer reminded everyone that despite its position at the rear of the pack leading the PD-(L)1 inhibitor charge, oncology is not all about immuno-oncology, and it has some pretty strong contenders in other parts of the anticancer armory (see cover story). In a pre-ASCO press briefing executives outlined the company's R&D and portfolio strategy in oncology, including why they out-licensed CAR-T to the former Kite Pharma executives, and gave a heads up about key presentations planned for the conference.

Over at Merck & Co, it's still very much about PD-1 inhibitor Keytruda, which unveiled strong results in first-line squamous non-small cell lung cancer, in combination with chemotherapy. The KEYNOTE-407 results open up another large chunk of the overall lung cancer market to Merck & Co and will be presented in more detail at ASCO. Nevertheless, the company faces competition from Roche, which will also be presenting data on its anti-PD-L1 drug Tecentriq in the first-line squamous NSCLC setting (see p11).

AstraZeneca is also beavering away to expand its PD-L1 inhibitor's position in the lung cancer market (see p12). It revealed new data showing an overall survival advantage in earlier-stage NSCLC patients taking Imfinzi, helping to take the sting out of a recent setback in a trial investigating Imfinzi in combination with its anti-CTLA-4 agent tremelimumab to treat NSCLC.

Lots more on ASCO next week from our two reporters at the conference, who will post regular updates on our website.

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Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: clientservices@pharma.informa.com

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christopher.keeling@informa.com

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Interview:
New Chugai CEO Lays Course As He Takes Reins
https://bit.ly/2IX4GlE

Chugai's new CEO Tatsuro Kosaka took up his position in March and is charged with taking the major Japanese company through the next stage of development as key products reach the global market and others begin to face biosimilar competition. In this first part of a two-part exclusive interview, he outlines the firm's vision, approach to R&D and how the strategic alliance with Roche is playing out.

Early-Stage Idiopathic Pulmonary Fibrosis (IPF) Candidates Race to Phase III
https://bit.ly/2kwwh2r

Multiple IPF drugs are being rushed into Phase III based on early-stage signals of efficacy and safety presented at the ATS meeting. Scrip spoke with the University of Pittsburgh's Kevin Gibson about the candidates, trial design, combination therapy and limitations of current therapy.

Dupixent Shines At ATS, But Experts Question Which Novel Biologic Physicians Will Choose
https://bit.ly/2ISP5aK

Phase III studies testing Dupixent in moderate-to-severe asthma were largely positive, but subgroup details raise questions about how it will compete against biologics targeting the IL-5 pathway. Some experts urge comparison trials to inform physicians' decisions about long-term use.

China JV Exit To Give Takeda More Focus, Cash
https://bit.ly/2GYUfMF

Takeda is selling its majority share in China biopharma joint venture Techpool to focus on its key growth areas in this market and raise cash ahead of the Shire acquisition, in a move that will also boost its former partner's presence in manufacturing and critical care.

Can Synthetic Vaccines Change The World's Approach To Infectious Disease Crises?
https://bit.ly/2LBWSY5

Emerging Company Profile: Emergex Vaccines will use its nanobody technology to develop entirely synthetic immunizations against the world's most concerning infectious diseases, including Ebola; evolving current options for vaccine stockpiling and national repositories.

inside:

Gilead May Have Better Takeover Targets Than Tesaro

KEVIN GROGAN kevin.grogan@informa.com

With the rumor mill once again trying to match up **Gilead Sciences Inc.** with PARP inhibitor specialist **Tesaro Inc.**, analysts at Datamonitor Healthcare's PharmaVitae team have been weighing up acquisition targets for the US biotech major that may make more sense.

In a new report evaluating potential takeover targets for the bigger players in the sector, PharmaVitae has highlighted Gilead as one of the firms likely to do more deals to further plug revenue declines in the hepatitis C market. It notes that the company "has a history of successfully pursuing leadership positions in new markets," exemplified by its $11bn acquisition of Pharmasset in 2012, a deal which was seen at the time as a huge risk but which placed Gilead as the dominant player in the HCV space, producing the mega-blockbusters *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir/sofosbuvir).

The boldest move Gilead has made to reduce its reliance on its HCV and HIV franchises came with its acquisition of CAR-T specialist Kite Pharmaceuticals in August 2017, followed by the purchase of Cell Design Labs in December 2017 for $567m. That deal brought in technologies that modulate gene expression of engineered T cells to Gilead's CAR-T products and this is the area that PharmaVitae believes Gilead will be most active in. *(Also see "Gilead Makes Cell Therapy The Base Of Its Oncology Platform With Kite Buy" - Scrip, 29 Aug, 2017.)*

The analysts have highlighted **Sangamo Therapeutics Inc.**, which they value in the region of $1.6bn, as a potential target, noting that Gilead is already paying $150m upfront in cash and up to $3.1bn in milestones plus tiered royalties on 10 drug candidates, derived from Sangamo's zinc finger nuclease and adeno-associated virus technologies.

PharmaVitae stated that combining Kite and Gilead's expertise and infrastructure with Sangamo could create a transformative leader in the genome editing/gene therapy/cell therapy field, noting that they view "off-the-shelf CAR-T technology as potentially game-changing." As such, it believes that **Cellectis SA**, which the analysts value at around $1.1bn, "presents the most appealing acquisition target out of the biotech companies pursuing the commercialization of CAR-T therapies," given that the French company's products utilize allogeneic technology, which facilitates off-the-shelf CAR-T therapies. *(Also see "Gilead Partners With Sangamo For Gene Editing As It Builds Up Kite's Cell Therapy Platform" - Scrip, 22 Feb, 2018.)*

Another area where Gilead is looking to lead is inflammatory liver disease and specifically non-alcoholic steatohepatitis (NASH). It has a number of candidates in the pipeline for the latter, led by selonsertib, an apoptosis-signaling kinase 1 (ASK1) inhibitor currently in Phase III trials, and it has bought NASH assets from **PheneX Pharmaceuticals AG** and **Nimbus Therapeutics** in the past few years. *(Also see "New Data Cast Doubt On Gilead's Phase III NASH Candidate Selonsertib" - Scrip, 20 Apr, 2018.)*

It is not surprising therefore that PharmaVitae has earmarked **Intercept Pharmaceuticals Inc.**, valued at $1.5bn, as a takeover target. The firm's *Ocaliva* (obeticholic acid), a farnesoid X receptor agonist, is one of the most advanced NASH treatments, having initiated Phase III trials back in 2015, although the analysts note that the FDA recently issued a warning regarding Ocaliva in relation to inappropriate dosing leading to liver-related deaths, "meaning the drug may lose market share to selonsertib after its approval." *(Also see "Intercept Makes No Changes To Ocaliva NASH Study Despite PBC Safety Issues" - Scrip, 25 Sep, 2017.)*

Another potential purchase in NASH could be **Madrigal Pharmaceuticals Inc.**, valued at $1.7bn. Its main asset is MGL-3196, a potential first-in-class oral thyroid hormone receptor (THR)-β agonist that reduces lipotoxicity and improves liver function and could enter Phase III in the third quarter of 2018. PharmaVitae also picked out **Genfit SA**, whose Phase III drug elafibranor "could be a lucrative asset for companies looking to diversify into a budding market." *(Also see "Madrigal's Early Phase IIb NASH Data Show Clinically Meaningful Fat Reduction" - Scrip, 6 Dec, 2017.) (Also see "Genfit May Be Gaining An Edge In NASH Race" - Scrip, 26 Oct, 2017.)*

Moving away from the liver, and potentially upping the purchase price, is **Galapagos NV**. Valued at $5.1bn, its lead product filgotinib is in Phase III trials for rheumatoid arthritis and has posted strong Phase II data showing it has a slightly more favorable side effect profile to other JAK inhibitors, while also showing greater reductions in hemoglobin – it is also in Phase II trials for six other indications including Crohn's disease, ulcerative colitis, Sjogren's syndrome and uveitis.

PharmaVitae noted that Gilead already owns a stake in filgotinib, after making a $725m payment in return for joint commercial rights to the drug. "A feature of the deal blocked Gilead making a takeover bid until 2018, meaning it may look to seize the opportunity when the block expires," the analysts noted, adding that a takeover would maximize Gilead's profits from filgotinib, "which has the potential to be a best-in-class treatment for autoimmune diseases." *(Also see "Galapagos Eyes Rare European Biotech Heavyweight Title, Launches $338m Offering" - Scrip, 18 Apr, 2017.)*

If Gilead is prepared to make a big dent in its bank balance, the PharmaVitae report suggested that **Incyte Corp.**, valued at $17.6bn, might be a target. It forecasts US sales of the JAK inhibitor *Jakafi* (ruxolitinib) to reach over $2.4bn in 2026 as the drug makes further inroads into its approved indications of myelofibrosis and polycythemia vera, and Incyte aims to expand Jakafi's label with approvals for essential thrombocythemia and graft-versus-host disease.

The analysts noted that the failure of Gilead's own JAK inhibitor momelotinib has sparked rumors, saying "there is mounting pressure on Gilead for a de-risked asset win and speculation has begun over potential Incyte takeover talks." They added that Incyte "looks more attractive after its market value considerably decreased" following the recent failure of epacadostat in the Phase III ECHO-301 study. *(Also see "Incyte/Merck's ECHO-301 Failure Casts More Shadow On IDO Space" - Scrip, 6 Apr, 2018.)*

As for Tesaro, it is par for the course that Gilead has been mentioned as a prospective acquirer. Tesaro's PARP inhibitor *Zejula* (niraparib) has a broad label for the maintenance treatment of ovarian cancer and possible future approvals in breast, prostate, non-small cell lung and bone cancers make it an attractive target, especially since its market capitalization has fallen from over $8bn to $3bn in the past year.

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Severe Asthma Market Snapshot: A Competitive Therapy Area That Will Test Payers' Influence

JESSICA MERRILL jessica.merrill@informa.com

The severe asthma market is in the midst of a paradigm shift with the launch of several new biologics that could change the standard of care for treating patients with uncontrolled disease.

The availability of several new treatment options is good news for the small, severely afflicted group of patients. But the launch of three interleukin-5 inhibitors for severe eosinophilic asthma and the expected launch of another drug, the IL-4/IL-13 blocker *Dupixent* (dupilumab) later this year with potentially broader applicability, has made the category hyper-competitive and it remains to be seen which drug maker will come out victorious with blockbuster-level sales.

The new drugs have caught the attention of payers too, because they cost significantly more than traditional inhaled respiratory drugs – the corticosteroids, long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) that have long been the standard of care for asthma. The new biologics can cost up to $32,000 to $40,000 per year, before rebates, while the cost of standard inhaled therapies is more like $5,000 to $6,000 annually.

By targeting drugs to the patients that really need them, drug makers believe they have a winning value proposition that payers will support. But as more options reach the market, payers could gain more influence over which drugs get the best access and may be able to negotiate steeper discounts.

"We are able to manage on label and reserve these typically for the patients that have extremely severe forms of asthma that are not being managed with cornerstone therapies," said Magellan Health's Steve Cutts.

New launches could present new opportunities for payers to contract for preferred drugs. Express Scripts Chief Medical Officer Steve Miller said he is optimistic there could be opportunities in the future for drugs in the category to compete more fiercely on price.

"We are going to put clinical first – we always do – but we believe there are going to be opportunities in the near future in this category," he said.

BIOLOGICS EXPECTED TO DRIVE GROWTH

Respiratory power players like **GlaxoSmithKline PLC** and **AstraZeneca PLC** hope their respective new biologics, *Nucala* (mepolizumab) and *Fasenra* (benralizumab) for eosinophilic asthma will help the companies extend their blockbuster tradition in the therapy area. **Teva Pharmaceutical Industries Ltd.** also is vying for market share with the IL-5 blocker *Cinqair* (reslizumab), though its product has some drawbacks versus the competition that have made it less of a competitive threat. **Regeneron Pharmaceuticals Inc.** and **Sanofi** will be newcomers to the respiratory space if Dupixent is approved for severe asthma as expected later this year.

Globally, biologics are expected to drive growth in the asthma market in the US, Japan and five major European markets from $12bn in 2017 to $18.9bn in 2026, according to Datamonitor Healthcare, even while inhaled respiratory drugs are expected to face their first generic competition. Biologic revenues in the seven major markets are expected to reach $7.3bn in 2026, Datamonitor forecasts, eventually outpacing sales of ICS/LABA drugs and becoming the highest grossing class in asthma.

The targeted patient population in severe asthma, competitive dynamics and growing push-back from payers over high-priced biologics present new challenges over what GSK and AstraZeneca experienced more than a decade ago with the launches of their respective blockbusters *Advair* (fluticasone/salmeterol) and *Symbicort* (budesonide/formoterol). Nonetheless, the drug makers have grown savvy when it comes to market access challenges, with the broader respiratory category coming under intense pricing pressure.

"We are in an era now where the number of options is much more expansive, and that's very good news for patients," GSK Senior VP-Respiratory and Pharma Operations Cheryl MacDiarmid said in an interview. Patients with severe uncontrolled asthma represent about 10% of the 25 million asthma patients in the US, but they account for a disproportionate share of the cost burden associated with asthma – about 50% of the total cost of asthma in the US, she said.

TARGETING THE RIGHT PATIENTS

Payers say they are open to new biologics for severe asthma, because they understand how sick patients are and how expensive their care can be. The third-party value assessment organization the Institute for Clinical and Economic Review (ICER) said it costs the US $50bn a year to treat asthma, with severe asthma accounting for 50% of the burden.

But payers also want to be sure the appropriate patients are getting the medicines. They are largely managing access in line with labeling for the drugs by measuring patient eosinophil levels, requiring prior authorization and step-through therapy with traditional inhaled respiratory drugs. In some cases, payers require confirmation the patient has been hospitalized in the last year due to their asthma.

"It's a little straightforward in that we are able to manage on label and reserve these typically for the patients that have extremely severe forms of asthma that are not being managed with cornerstone therapies," said Steve Cutts, vice president of pharmacy services and clinical strategy for the pharmacy benefit manager **Magellan Health Services Inc.**

GSK, thus far, has a leg up in the space. The UK drug maker was the first to market with an IL-5 inhibitor, with the approval of Nucala by the FDA in November 2015. It is approved as an add-on therapy for patients with a specific type of asthma with an eosinophilic phenotype. It was the first new biologic to launch for asthma since **Roche**'s *Xolair* (omalizumab) was approved more than a decade before in 2003.

Xolair is an antibody that binds to human immunoglobulin E (IgE) and is approved for allergic asthma. Xolair got off to a slow start initially, but the brand has picked up steam as knowledge of the molecular underpinnings of asthma have evolved. It crossed the blockbuster threshold in 2014 and has continued to grow by double-digits since. It generated $1.74bn (CHF1.74bn) in 2017 sales.

Nucala and the other IL-5s that have followed – Teva's Cinqair in March 2016 and AstraZeneca's Fasenra in November 2017 – are indicated specifically for eosinophilic asthma.

All three IL-5 drugs work through the same mechanism of action, but have differences that could be commercially advantageous. Nucala and Cinqair target the Il-5 ligand, while Fasenra targets the IL-5 receptor. Cinqair, for example, is dosed via intravenous infusion administered by a health care professional over 20 to 50 minutes every four weeks, while Nucala and Fasenra are administered via a faster subcutaneous injection, Nucala every four weeks and Fasenra every eight weeks. Cinqair also has a boxed warning about risk of anaphylaxis and a requirement for observation upon administration, while Nucala and Fasenra do not. Teva was hoping to launch a subcutaneous version of Cinqair, but a Phase III trial testing the formulation failed earlier this year.

AstraZeneca believes its eight-week dosing regimen will give it a competitive advantage in the crowded market. *(Also see "AZ Looks To Lead Severe Asthma Market After US Fasenra OK" - Scrip, 15 Nov, 2017.)"*

"So far, we are really happy with the initial launch in the US. It's going really well, in line with what we expected," AstraZeneca's Executive Director, Biologics Respiratory Marketing Mina Makar said in an interview. Fasenra generated $21m in the first quarter, its first quarter on the market. Nucala, meanwhile, generated £104m ($139.4m) in the first quarter and £344m ($461.3m) in 2017. Teva hasn't broken out sales of Cinqair, which usually is an indication the results are not material to earnings.

AstraZeneca has its work cut out for it if Fasenra is going to catch up to the first-to-market Nucala, but management insisted it still is early days for the burgeoning category of drugs.

"Of the patients that are severe uncontrolled asthmatics, today only 15% of them that need a biologic are being treated with one," Makar said. "The population is big and the unmet need is high and not enough patients are being treated."

GSK's MacDiarmid agreed there is a lot of room for growth in the category. About 20,000 patients in the US are on Nucala, while there are some 300,000 patients with severe asthma.

ENTER DUPIXENT

GSK and AstraZeneca won't have an edge in the market for long, because Regeneron/Sanofi's Dupixent is pending at FDA for severe asthma, with an action date of Oct. 20. Dupixent has shown strong efficacy and good safety in patients with severe asthma in Phase III studies, and it could target a broader patient population of severe asthmatics beyond those with eosinophilic asthma, which could make it a significant competitive threat.

"The IL-4/13 pathway appears to be the master regulators for the Type 2 inflammatory response. This Type 2 response impacts multiple different cell types. It's not just a single cell type like eosinophils," explained Regeneron's Senior VP/Head of Global Clinical Development David Weinreich. "In general, Type 2 asthma tends to be on the more severe side, because there are a lot of different cellular components, and dupilumab blunts that entire cascade."

Dupixent already is on the market, approved for the treatment of atopic dermatitis in March 2017.

In asthma, Regeneron and Sanofi previously presented top-line data from the pivotal programs under the LIBERTY Phase III trials showing treatment with dupilumab reduced exacerbations and improved lung function in severe asthma patients when added onto maintenance treatment. *(Also see "Dupixent FDA Asthma Review Bolsters Sanofi And Regeneron" - Scrip, 2 Mar, 2018.)*

More detailed Phase III data presented at the American Thoracic Society's International Conference in San Diego May 18-23 and published in the *New England Journal of Medicine* raised some questions, however, about how differentiated the product might be from the IL-5 biologics.

WEIGHING PRICE AND VALUE

Regeneron wouldn't comment on pricing plans for Dupixent in asthma, or say whether or not the drug would be priced the same as it is for atopic dermatitis, as is generally how pharmaceutical manufacturers handle pricing drugs for multiple indications. The wholesale acquisition cost of Dupixent for atopic dermatitis is $37,000 per year. That cost wouldn't be out of the ballpark from the competition, particularly if it was offset with rebates. The dosing in atopic dermatitis is in line with what was studied in asthma, 300mg and 200mg every other week after an initial loading dose. The recommended dosing for atopic dermatitis is 300mg every other week.

"Our argument to the regulators and our argument to the payers are going to be the same," Weinreich said. "In this group of patients that we have already curated to be very high in a Type 2 component, there is a huge unmet medical need, and the combination of decreasing exacerbations, improving lung function, decreasing that year-over-year decline in FEV1, is a unique triplet."

Fasenra is priced at an annual wholesale acquisition cost (WAC) of $28,000 to $33,000, depending on the dosing administration dates. In the first year, it costs $38,000 because of an additional loading dose. The WAC for Nucala is around $34,000 per year.

Despite multiple drugs that work through a similar mechanism of action, the therapy area hasn't experienced a high level of competitive rebating as has been experienced in the inhaled respiratory space, at least for now, according to drug manufacturers and payers. Payers generally are more reticent to restrict access in specialty categories though that is changing as specialty drug spending continues to mount and payers look for ways to curb costs. .

ICER also is weighing in on the category as the competitive dynamics intensify. The third-party drug pricing reviewer announced May 15 that it will evaluate the comparative clinical effectiveness and value of biologic treatments for asthma, including Xolair, Nucala, Fasenra, Cinqair and Dupixent. ICER previously reviewed Nucala and determined in a 2016 final assessment that the price did not represent a fair value and that a substantially discounted price of $7,787 to $12,116 would be more appropriate.

It will be interesting to see how Sanofi and Regeneron will respond to the ICER review. The partners have taken a more proactive approach of collaborating with ICER on other drug reviews, including on the cholesterol-lowering drug *Praluent* (alirocumab), for which the companies agreed to lower the price of the drug in line with ICER's value assessment earlier this year for payers that agreed to remove access restrictions. *(Also see "Praluent Pricing: Collaboration With ICER Sets A New Standard" - Scrip , 12 Mar, 2018.)* Some investors at the time were alarmed the companies might have set a precedent for accepting ICER's determinations on future drugs, though management disagreed. The companies also worked closely with ICER on Dupixent ahead of the launch for atopic dermatitis in 2017.

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Dova's Doptelet Gets First-To-Market Edge In Thrombocytopenia, Ahead Of Shionogi

JOSEPH HAAS joseph.haas@informa.com

For a CEO of a company obtaining its first drug approval and preparing to replace an entrenched standard of care with a new one, **Dova Pharmaceuticals Inc.** CEO Alex Sapir presents a picture of extreme confidence, saying physicians have expressed enthusiasm that *Doptelet* will offer an oral drug therapy alternative to platelet transfusions for increasing patients' platelet counts.

The Durham, N.C.-based firm obtained US FDA approval of Doptelet (avatrombopag) May 21 to treat low blood platelet count in adult chronic liver disease patients who are scheduled to an invasive procedure such as surgery. The oral thrombopoietin receptor agonist becomes the first drug therapy approved for this indication, although **Shionogi & Co. Ltd.**'s lusutrombopag is only a few months behind, with an Aug. 26 PDUFA date. The latter was approved in Japan under the brand name *Mulpleta* in 2015. (*Also see "Japan First To Approve Omarigliptin, Lusutrombopag" - Scrip, 30 Sep, 2015.)*

Despite the challenges inherent in supplanting an established standard of care, Sapir told *Scrip* he expected Doptelet will do so "with relative ease."

"My experience has been that the more compelling your offering is compared to the current standard of care, the more likely you are to be able to successfully make that paradigm shift," he said. "The feedback we've been hearing from physicians is that the profile of Doptelet is a dramatic improvement from the current standard of care, platelet transfusions, because not only do you have a drug that can very reliably increase platelets to a level above which physicians feel comfortable doing a procedure without the risk of bleeding, but you're able to [do so] without all of the risks currently associated with platelet transfusion."

These risks include the potential for antibody formation, which can render platelet transfusions ineffective following significant use in a patient. Sapir cited reports that up to 50% of patients who receive repeated platelet transfusions to reduce bleeding risk can develop such antibodies. Physicians have told Dova "that's a big deal," the exec added.

Doptelet obtained FDA approval on May 21 with what analysts called a clean label. The label includes no black box warning to hepatotoxicity and warns only of the potential for thrombotic complications in high-risk patients. The drug is approved in daily 40 mg and 60 mg doses – depending on the patient's platelet count – for five days of therapy.

ADVANTAGES COMPARED TO SHIONOGI CANDIDATE

By contrast, Shionogi's lusutrombopag was studied in Phase III with a five-day dosing period, but the with possibility for additional doses on days six and seven, as needed. According to Jefferies Equity Research analyst Eun Yang, 66% of Phase III patients ended up needing seven days of treatment, offering Dova another advantage beyond its first-to-market status. In a May 21 note, Yang also pointed out that Doptelet yielded better clinical data in patients with lower platelet counts as baseline, although not in a head-to-head comparison.

Jefferies estimates a peak US sales potential of $630m for the drug, assuming additional indications, and based on a model of 70,000 eligible patients undergoing between one and three medical procedures per year and a treatment cost of $9,000 per patient. Dova intends to initiate a Phase III registrational study this quarter to add chemotherapy-induced thrombocytopenia to the drug's label. Designed as a 120-patient study, the trial is expected to produce data in about two years.

On an investor call May 21, Dova reported that it has put a commercial team in place, plans to launch the drug in June and will reveal pricing at that time. Sapir told *Scrip* the force will number about 30-60 total reps. The team in place has more than 300 aggregate years of detailing in the liver disease area, he added. "These people have deep relationships with the existing hepatologists," Sapir said.

Dova's commercial plan is to leave the hospital setting to the transfusion SOC, while focusing on the outpatient setting. "This is not going to be considered a hospital product, so the good news there is that we don't have to go to the tens of thousands of hospitals and try to get this drug on the hospital formulary," Sapir said. "The drug will ultimately be used by the hepatologist but in an outpatient setting." Dova's commercial team has already done a lot of pre-commercial negotiating for formulary access with pharmacy benefit managers and other payers, he added.

The company pursued the chronic liver disease setting first because that patient base represents the largest share within those who need platelet therapy prior to a medical procedure, Sapir explained. Dova estimates that 1.2 million platelet transfusions are done annually in the US, with roughly half occurring in an emergency-type setting. The company's goal is to target that other half in which platelet therapy proceeds on a planned basis, he said.

Beyond chronic liver disease, Dova envisions chemotherapy-induced thrombocytopenia as the second-largest opportunity in this market, Sapir said. "We know that there are certain chemotherapies in which thrombocytopenia occurs in up to 70% of cases," he noted. "What physicians currently are doing is either giving a platelet transfusion or alternatively reducing the dose of chemotherapy, skipping a cycle of chemotherapy or delaying a cycle of chemotherapy."

Leerink Partners models revenues of $21m for the drug this year, analyst Geoffrey Porges wrote on May 22. This could grow to about $341m in 2025 with the current label, he added, but additional indications could provide further upside.

Dova's plan to is to go it alone in the US with commercialization, while seeking a partner for ex-US commercialization of the drug. It has been filed for approval in the EU and Dova expects a decision by June 2019, Sapir said.

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CONTINUED FROM COVER

As for the third prong, it encompasses the next wave of innovation in immuno-oncology, which is focused on finding the right combination of therapies. Pfizer is looking at combinations of its PD-L1 inhibitor *Bavencio* (avelumab), which it gained through a partnership with **Merck KGAA**, with targeted agents such as Pfizer's *Inlyta* (axitinib) and talazoparib, and a triple combination with OX40 and 4-1BB, co-stimulatory receptors on T cells.

AIMING FOR FIVE BLOCKBUSTERS

Mikael Dolsten, president of Pfizer Worldwide Research and Development, noted that Pfizer had been pursuing a step change in R&D productivity, and oncology products now comprise the top five of 15 actual and expected blockbuster drugs at the company. The company's oncology revenues grew 33% to $6.06bn in 2017, powered by Ibrance and Xtandi.

"Beyond this we have numerous opportunities to generate additional compelling clinical data with other [new molecular entities (NMEs)]," Dolsten said. He noted that Pfizer has new approaches to deal with drug resistance in estrogen receptor-positive breast cancer, including a new generation of CDK inhibitors and a triple combination containing gedatolisib. The latter is in a Phase 1b study.

In the prostate cancer area, he said Pfizer recently started clinical trials with an epigenetic agent targeting EZH2 and has a cancer vaccine with a new platform for prostate cancer. In addition, Dolsten said the company planed within the next nine to 12 months to start clinical trials with nanoparticles containing small molecules targeting resistance mechanisms in prostate cancer.

Pfizer doubled down in oncology investment under the leadership of CEO Ian Read and gained some credibility with the launch of Xalkori, but it was the launch of Ibrance in 2015 that gave Pfizer a powerful revenue generator in oncology. Ibrance accounted for more than half of Pfizer's oncology sales in 2017 and has grown into one of Pfizer's top three brands behind the *Prevnar 13* pneumococcal vaccine and the pain drug *Lyrica* (pregabalin). It was one of the most commercially successful oncology launches over the last 12 years. *(Also see "The Most Successful Oncology Launches Of A Decade" - Scrip, 28 Feb, 2018.)*.

The renal cancer drug *Sutent* (sunitinib) is another blockbuster, as is Xtandi, which Pfizer gained with its $14bn acquisition of **Medivation Inc.** in 2016, though Pfizer shares profits and revenue with **Astellas Pharma Inc.** in the US and receives royalties on sales outside the US.

The company's third anchor oncology drug is the PD-L1 inhibitor Bavencio, which is approved for Merkel cell carcinoma and bladder cancer. Pfizer and Merck split profits generated by Bavencio under their collaboration, though the companies have struggled to get their footing in the competitive anti-PD-1/PD-L1 market behind the early leaders **Bristol-Myers Squibb Co.** and **Merck & Co. Inc.**

PFIZER ON ITS DECISION TO OUT-LICENSE CAR-T

Pfizer is interested in immuno-oncology beyond its focus on immune checkpoints, including chimeric antigen T cell receptor (CAR-T) therapies, vaccines and small molecule combinations. But the company recently outsourced its CAR-T programs to former **Kite Pharma Inc.** executives, who formed the start-up **Allogene Therapeutics Inc.** with Pfizer's research team. *(Also see "'We Jumped' At Opportunity To Take On Pfizer's CAR-T Program, Allogene's Chang Says" - Scrip, 4 Apr, 2018.)*

Pfizer's Robert Abraham, senior VP and group head of oncology R&D, who attended the press briefing by phone, explained the company's decision to create the company with the ex-Kite group. He noted that Pfizer had done considerable work with the allogeneic CAR-T platform, which it acquired and developed in collaboration with **Cellectis SA**, and recognized that there were obstacles going forward.

"We felt that the CAR-T platform, the development of this platform and the transition into solid tumors, would best be handled by a group that had one mission, that is to make CAR-T a viable therapy for solid tumors," he said.

Abraham said that breaching the solid tumor barrier is going to present challenges that largely have not been encountered in the hematologic malignancy space. He said the engineered T-cells would encounter a very immunosuppressive space and that the dominant immunosuppressive factors have to be identified. Another important challenge, he said, was the paucity of solid tumor antigens.

"In order to have a safe CAR-T cell, one needs to identify antigens that are selectively expressed or highly over-expressed on tumor cells relative to normal cells in the body to generate a sufficient therapeutic index to have an effective therapy," Abraham said.

With experienced leadership at companies like Allogene, "I think we'll see over the next five to 10 years a very good chance that CAR-Ts will enter into the solid tumor space in a big way," he added.

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Sanofi In Pole Position In Oral Type 1 Diabetes With Zynquista Filings

KEVIN GROGAN kevin.grogan@informa.com

Shutterstock: Chen WS

The US FDA has begun its review of **Sanofi** and **Lexicon Pharmaceuticals Inc.**'s *Zynquista* (sotagliflozin), raising the firms' hopes that it will be the first oral drug approved to treat adults with type 1 diabetes.

The agency has accepted Sanofi's regulatory filing as an add-on to insulin injections to help improve blood sugar control in type 1 diabetes patients. The submission, which comes after a filing in Europe at the end of March this year, has a Prescription Drug User Fee Act (PDUFA) target date of March 22, 2019.

Both of the Zynquista filings are based on data from the inTandem clinical trial program which includes three Phase III studies assessing the oral dual inhibitor of the SGLT-1 and SGLT-2 proteins in approximately 3,000 adults with inadequately controlled type 1 diabetes. The third study showed that Zynquista combined with optimized insulin therapy is superior to placebo with the same background therapy in controlling A1c levels, with no episodes of severe hypoglycemia or diabetic ketoacidosis (DKA) reported following randomization.

The safety profile is seen as key to Zynquista's success, with the rationale being that dual inhibition of SGLT1 and SGLT2 results in fewer side effects relative to the currently available SGLT2 inhibitors, such as **Eli Lilly & Co.**/**Boehringer Ingelheim GMBH**'s *Jardiance* (empagliflozin) and **AstraZeneca PLC**'s *Forxiga/Farxiga* (dapagliflozin). Those two are only marketed for type 2 diabetes and although they are being studied for type 1, they are some distance behind Zynquista in that indication. (*Also see "AZ Sees A Future For Forxiga In Type 1 Diabetes" - Scrip, 6 Mar, 2018.*)

In an investor note, analysts at Wedbush Securities noted the "stellar safety and efficacy results" from the three inTandem trials. Given that sotagliflozin is a new chemical entity and could be the first oral treatment for type 1 diabetes, they anticipate a potential FDA advisory committee meeting in the second half of 2018 with possible approval before the anticipated PDUFA date.

If approved, they project gross peak US sales for Zynquista of about $1.35bn in 2024 assuming launch in the first half of next year. They forecast European peak sales of $565m in 2025, assuming a second half 2020 launch.

Before the filings, Kevin Shannon, an analyst with Datamonitor Healthcare, told *Scrip* that Zynquista has the potential to meet several unmet needs in the type 1 diabetes market, and will likely achieve significant commercial success based on its first to market status, if approved. He added that "the drug's ability to improve glycemic control, potential to reduce insulin dose, and association with weight loss make it very attractive to physicians treating type 1 diabetes."

However, he also noted that concerns over increased risk of DKA with the SGLT class as a whole remain and if approved, Zynquista may contain a warning on its label stating that risk. This has the potential to slow the drug's initial growth,"although this is expected to be overcome by its several benefits and the lack of non-insulin alternatives in type 1 diabetes."

Sanofi is hoping that Zynquista, which is also in trials for type 2 diabetes with Phase III results due in 2019, will help fill the gap in revenues that the French drugmaker is suffering with the continuing decline of its off-patent diabetes blockbuster *Lantus* (insulin glargine). The latter brought in €911m in the first quarter, down 17.7%, while Lantus sales sank 31.1% to €413m in the US, battered by lower prices and the loss of Medicare Part D business. *(Also see "Dupixent Dip Dogs Sanofi Efforts To Deal With Diabetes Decline" - Scrip, 28 Apr, 2018.)*

Zynquista is arguably more important to Lexicon, which is entitled to 40% royalties of net sales for type 1 diabetes in the US under the terms of a co-promotion option with Sanofi and low double-digit royalties in Europe. Its first product – *Xermelo* (telotristat ethyl) – was approved in the US in February last year as the first drug therapy given the thumbs-up for carcinoid syndrome but Zynquista is expected to be Lexicon's main growth driver.

Wedbush noted that Lexicon ended the first quarter of 2018 with about $262.3m in cash and the broker projects sufficient runway to support Xermelo and Zynquista and achieve full-year profitability in 2020. "We see significant potential upside for Lexicon and the potential for acquisition," it concluded.

Sanofi licensed sotagliflozin from Lexicon in 2015 for $300m upfront and up to $1.4bn in development, regulatory and sales milestone payments plus royalties.

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Tomorrow's CRO Steps Into The Real World

JO SHORTHOUSE joanne.shorthouse@informa.com

Some of the industry's biggest players have used M&A activity to grasp the big data nettle, driven by the ongoing emphasis on outcomes and value-based care. The merger of INC Research and inVentiv Health in an all stock $4.6bn deal to become Syneos Health is one of the latest and largest illustrations of an outsourcing trend that reflects the specialist evidence needed for the successful launch of a new product. In other words; real-world evidence.

Data-Driven Deals

Buyer	Acquisition Company	Value	Date Completed
PPD	Evidera	Undisclosed	September 2016
IMS Health	Quintiles	$9bn	October 2016
INC Research	inVentiv Health	$4.6bn	August 2017
ICON	Mapi Group	Undisclosed	July 2017
PRA Health Sciences	Symphony Health Solutions	$530m	September 2017

Source: Company reports

DATA DEFINES DEVELOPMENT

The investment house Jefferies conducts a pharma services survey which, this year, revealed that 28% of respondents believe big data is the largest opportunity to improve drug development. In line with that belief, 50% of respondents believe QuintilesIMS (now IQVIA) has developed the most compelling strategy to improve patient recruitment (up from 34% in 2016).

"We believe the development of big data, predictive analytics, and digital technologies will define the trajectory of drug development over the next 5-10 years," the survey states. "That best positions CROs that have already started investing and developing tools that will make them a core, strategic partner to biopharma clients." This sentiment favors IQVIA, PRA Health Services, ICON, and Syneos Health, all of which are using real world data through acquisition, merger and partnership, as the outsourcing market realizes the necessity of analytics to improve efficiency in drug development.

While the adoption of big data has been an ongoing theme in the CRO industry for the last few years, it seems that through M&A activity, CROs are incorporating real change. The largest example of this is undoubtedly Quintiles' merger with IMS, but we've also seen PRA Healthcare launch its Predictivv platform and subsequently buy data analytics company Symphony in September 2017 for $530m. ICON's partnership with IBM Watson, EHR4CR and TriNetX allow for the leveraging of millions of de-identified patient records from integrated research networks to instantly locate suitable participants, identify optimal study sites, and iteratively refine trial protocols in real-time. However, there is more to be done.

David Windley, Managing Director of Jefferies' Healthcare Equity Research team, says: "All the CROs, apart from Syneos and IQVIA, need to become more relevant in real-world evidence. They need to continue to build up capabilities in that space," he explains. "The challenge here is that most of this is a new and evolving space, it's an increasing regulatory requirement and that begets for-profit pursuit of a business opportunity."

In the last 18 months, each of the seven largest companies (IQVIA, Parexel, PPD, LabCorp/Covance, PRA Health, Syneos and ICON) have seen a change in their business mix. Windley observes: "The top seven are the companies that have started to invest in post-approval capabilities and have the financial wherewithal to do it. They recognize the need to grow in that area and they also recognize that the real-world evidence area is growing quickly. It's growing quicker than Phase II/III, but it's not doubling. It's not like a technology growth curve, it's not like the adoption of the iPhone, it's a mid-teens growth area. It will grow, but at a moderate pace."

SPONSOR SENTIMENT

Of course, consolidation should mean less choice for biopharma's decision makers when debating the various merits of service providers. It could also mean that a nimble service area, lauded for its ability to perform adaptive trials, could become slightly more sluggish while internal engines chug, especially when it comes to adopting new technology. The sprightly hand of the slow-moving pharmaceutical beast may become slightly more hampered as companies continue to scale up.

Nevertheless, in its most recent outsourcing survey, Jefferies found that 55% of its pharma respondents indicated that they viewed CRO consolidation positively. Within large pharma, that increases to 74% with the primary reason being increased CRO scale. It seems the traditional view of CRO consolidation being disruptive, in case of project and staff turnover, may no longer be the case.

Having a drug development partner at the forefront of big data gathering and utilization is imperative for a sponsor. However, it seems that these biopharma clients are less likely to acknowledge the differences in CRO data offerings than investors are. "When I talk to biopharmaceutical sponsors, and ask them about data strategies in the CRO space, the answers I get are surprisingly dismissive," recalls Windley. "The customers seem to not perceive much difference or they are so inundated with different sales pitches from the various CROs that they don't really feel like there's a lot of differentiation."

"Investors are always trying to work out how companies within a peer group are different and how do they differentiate themselves to their customers," says Windley. "And right now, investors perceive a bigger differentiation than customers do."

MARKET DOMINANCE

With drug naïve patient populations harder to find and inclusion/exclusion criteria becoming more specific, especially in the case of rare disease and orphan drugs, more drugs are being approved with post-marketing requirements. The increased requirements from the payer environment and the regulator environment to surround a drug with contextual evidence about how this drug is going to deliver value, and how it's going to be used in real practice, means that the strategies of larger CROs to buy boutique data businesses is a trend likely to remain.

"Everyone agrees that we like innovation," says John Kreger, Partner at William Blair. "But we're also uncomfortable with how much it costs a consumer. The way to have both of those things dealt with is to have more drugs developed and approved in a timely way without lots of failures. There is a big effort to do that and that's why we view this as a long-term structural trend."

The CRO industry has always been dominated by a handful of large companies with a large range of capabilities. The use of technology and data in drug development is still, in the grand scheme of things, very new. And as such no major technology provider or CRO has staked out their claim to lead the space.

"I think you have two companies that have said that they believe in this trend and will put significant resources behind it, and that's IQVIA and PRA Health," observes Kreger. "But what we've seen from the CRO industry over the last 20-30 years is a gradual market share consolidation trend."

CROs are people businesses, and have succeeded because of their agility in comparison to their clients. Size, in an industry like that, can be a detriment, Kreger explains. "If some time in the future technology becomes a key differentiator, rather than people, then maybe you can get a leadership position," he states. However, he does not think this is the case for the clinical outsourcing market, at least not for some time. In some industries there are very dominant companies that have a stranglehold on providing capability. "I don't think that's the case," he says. "There are five or six really impressive companies in this space and that won't change, at least not for the next 10 years."

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Merck's Stellar Keytruda Squamous Lung Cancer Data Refute Naysayers

EMILY HAYES emily.hayes@informa.com

Merck & Co. Inc.'s announcement that its PD-1 inhibitor *Keytruda* combined with chemotherapy demonstrated overall survival and progression-free survival benefits in the KEYNOTE-407 study in first-line squamous non-small cell lung cancer (NSCLC) support the drug's role in this indication and dominance in the tumor type generally.

Merck announced May 23 that the combination of Keytruda (pembrolizumab) and chemo demonstrated benefits for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS) versus chemotherapy alone in an interim analysis of the KEYNOTE-407 study, which enrolled 560 patients with the metastatic squamous type of NSCLC. Safety was consistent with results previously reported in lung cancer, the company reported.

Full results will be presented at the American Society of Clinical Oncology (ASCO) annual meeting, to be held June 1-4 in Chicago.

NSCLC is the most valuable tumor type for PD-1/L1 checkpoint inhibitors, accounting for almost half of the immunotherapy class's projected $30bn in sales for 2022, according to Morningstar Research estimates. About one third of NSCLC is the squamous type.

So far, Merck has managed to dominate in the valuable lung cancer indication as the only drug approved as a first-line therapy for NSCLC.

Keytruda is approved as a monotherapy for first-line treatment in NSCLC patients with PD-L1 expression of 50% or more and second-line NSCLC for those with at least 1% PD-L1 expression. A combination of Keytruda with chemotherapy is approved for first-line non-squamous NSCLC.

Now, with the interim KEYNOTE-407 analysis, Merck may now unlock Keytruda's access to the squamous population in first-line NSCLC.

However, detailed data for **Roche**'s competing *Tecentriq* (atezolizumab), a PD-L1 inhibitor, in the IMpower 131 study also are due to be presented in a late-breaker session at the ASCO meeting, following a topline release, setting off a showdown in squamous NSCLC, not to mention a battle for the first-line setting non-squamous NSCLC that also is likely to take place at the meeting.

Merck had announced on May 3 that it filed the Keytruda/chemo combination in first-line squamous NSCLC with the US FDA ahead of the PFS and OS data presentation at ASCO based on secondary endpoint response rate data.

This followed a report of positive response rates in an early cohort of participants in the KEYNOTE-407 study on May 1. At the time, there were fears that the company was hiding negative survival results and banking on response rate data, a lower standard. *(Also see " Merck's Keytruda Keeps Nipping At Opdivo's Heels" - Scrip, 1 May, 2018.)*

But the company went on to show its confidence in the combination by announcing the filing based on ORR data.

At the time of investor skepticism, a number of analysts, including Evercore ISI's Umer Raffat and Bernstein Research's Tim Anderson, however, had been confident about Keytruda in squamous NSCLC and reassuring that the negative investor reaction regarding KEYNOTE-407 was overdone and that the results were likely positive.

LATEST REACTION

Some analysts were exuberant on the latest news on May 23 of a survival benefit, although the full presentation awaits at ASCO. In a May 23 note, Credit Suisse's Vamil Divan commented that combined with non-squamous NSCLC, the KEYNOTE-407 squamous success locks down a massive first-line opportunity in NSCLC.

"We already knew Keytruda showed a benefit on overall response rate (ORR) in 407, but prolonging survival is obviously what matters," Divan said.

The fact that PFS and OS were both statistically significant at the first interim evaluating these endpoints is particularly positive because it is indicative of a clinically meaningful benefit, similar to what was seen in the KEYNOTE-189 study of non-squamous NSCLC, the analyst said.

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PACIFIC Pays Off Again For AZ With Imfinzi Lung Cancer OS Success

KEVIN GROGAN kevin.grogan@informa.com

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Fresh data from the key PACIFIC trial showing that *Imfinzi* (durvalumab) significantly improves overall survival (OS) in patients with earlier stage non-small cell lung cancer (NSCLC) has placed **AstraZeneca PLC** further ahead of the chasing checkpoint inhibitor pack in this indication.

The company has announced that a planned interim analysis conducted by an independent data monitoring committee concluded that the Phase III PACIFIC trial has met the second of two primary endpoints by showing statistically-significant OS benefit compared to placebo in patients with unresectable (ie inoperable) Stage III NSCLC whose disease had not progressed following platinum-based chemotherapy concurrent with radiation therapy. The results, which will be presented at a forthcoming medical meeting, follow progression-free survival (PFS) data unveiled at last year's European Society for Medical Oncology congress in Madrid, which showed that patients taking the PD-1/L1 inhibitor lived on average 16.8 months without their disease worsening, compared with 5.6 months for those on placebo.

The PFS benefit led to US regulatory approval in February, and in Canada earlier this month, making Imfinzi the only immunotherapy that has the green light in this setting. Three rival PD-1/L1 drugs – **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), **Roche**'s *Tecentriq* (durvalumab) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) are approved for NSCLC, but for the metastatic stage IV of the disease. *(Also see "AstraZeneca's Imfinzi Scores First Early Lung Cancer Approval" Scrip, 16 Feb, 2018.)*

The stage III market is a wide one which AstraZeneca says represents approximately one-third of NSCLC incidence, affecting around 105,000 patients in the top eight countries (China, France, Germany, Italy, Japan, Spain, the UK and US) in 2017. The majority of them are diagnosed with unresectable tumors and the company noted that before PACIFIC, the standard of care was chemotherapy and radiation therapy, followed by surveillance to monitor for progression.

Analysts agreed that the news is a major plus for AstraZeneca. Deutsche Bank issued a same-day investor note May 25 saying it was somewhat expected, "given exceptionally strong PFS data already presented," but confirmation of an OS benefit "is particularly important in a potentially curative setting such as Stage III lung cancer." The broker added that "this is likely to compel physicians to integrate Imfinzi quickly into practice and will be important to AstraZeneca's efforts to drive further penetration of concurrent chemo-radiation in this setting.

The analysts added that "the data raises the bar for future competition, which may struggle to reproduce this benefit given emergence of Imfinzi as standard of care and increasing use of PD-1 inhibitors in first-line metastatic disease. "What is more, that competition is a long way behind.

COMPETITION WAY BEHIND

Deutsche Bank does not believe AstraZeneca will face competition from other PD-1/PD-L1s before 2020, noting that the closest rival in this setting is Bristol, which initiated a trial of Opdivo in locally advanced, unresectable lung cancer in October 2016. Data from that study are unlikely before the second half of 2019.

Analysts at Jefferies issued a note saying that "whilst we still have to wait to see details of the absolute benefit, this should further reinforce Imfinzi's leading position." Noting that the PACIFIC OS read-out is earlier than expected, with AstraZeneca having previously indicated it was not anticipated until 2019, the team agreed that "any potential competitor data is still some some way off," while Morgan Stanley issued a note saying it believed Imfinzi had at least a 24-month start on any rivals.

Imfinzi has got off to a strong start even without the OS data on the label. The US approval for NSCLC – the drug's first green light was for the much smaller bladder cancer indication – helped first-quarter 2018 revenue grow to $62m, up 344% compared to the fourth quarter of last year. The company confirmed on the first-quarter earnings call that nearly all of those sales are in lung and Imfinzi is now 50% penetrated into the unresectable stage III lung cancer market in the US for patients receiving chemo-radiation therapy. *(Also see "AstraZeneca Q1: Tagrisso Beats Expectations And Drives Oncology Performance" - Scrip, 18 May, 2018.)*

However, in its note, Deutsche Bank pointed out that only 50% of patients receive this "and AstraZeneca is now focused on driving further uptake of this modality." With IMS weekly sales already annualizing at around $480m, "this implies a $1.8bn market in the US alone," the analysts added.

The PACIFIC OS data is a boost given the setback Imfinzi suffered last month with the failure of the ARCTIC study, which looked at the drug in combination with AstraZeneca's investigational anti-CTLA-4 agent tremelimumab. The combo failed to produce either a progression-free or survival benefit when used in the late-stage treatment of advanced NSCLC patients. *(Also see "ARCTIC Chill Descends On AstraZeneca's Imfinzi/Treme Combo In NSCLC" - Scrip, 24 Apr, 2018.)*

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Astellas Culls Positions Ahead Of Big Expiry

IAN HAYDOCK ian.haydock@informa.com

Astellas Pharma Inc. is offering early retirement incentives to up to 600 employees in Japan as it rolls out a new mid-term plan that emphasizes "optimizing organizational capabilities" and prepares for a key patent expiry in the US.

Although not explicitly mentioned in either the restructuring or business plans, the major Japanese firm is facing the first loss of US exclusivity next year for its big-selling urology drug *Vesicare* (solifenacin). The muscarinic antagonist, used in overactive bladder, brought in JPY125.7bn ($1.15bn) globally in the most recent fiscal year to March 31, around 40% of which was from the Americas region.

In Japan too, some older major products such as *Micardis* (telmisartan) are coming under increasing generic pressure.

Helped by new launches and other cost savings, the Japanese firm sees core operating profit under its new Strategic Plan 2018 improving by more than JPY30bn in fiscal 2020 (ending March 31, 2021) over the JPY268.7bn last year, and a core operating profit margin of 20%.

The mid-term blueprint, just unveiled by president and CEO Dr. Kenji Yasukawa, emphasizes sustainable growth through innovative science to provide value to patients, with a focus on maximizing key global products and progression of the late-stage pipeline.

SUBSIDIARY CLOSURES

Astellas in Tokyo told *Scrip* that the restructuring was being taken as it seeks to align its core operations across all group companies in Japan under the new plan.

At a press briefing, Yasukawa said the decisions formed part of a broader strategic "focused area approach" Astellas has been pursuing for several years, also conceding that "immediately after that [the Vesicare expiry] no drugs will be put into place, so…a [sales] loss will be fulfilled."

The changes will see the discontinuation of all operations at several Japanese subsidiaries including Astellas Research Technologies (with around 200 staff) and Astellas Marketing and Sales Support (around 70), and most activities at the Astellas Learning Institute (around 80 employees) by the end of the current fiscal year.

The Astellas Analytical Science Laboratories is also being divested to the French analytical testing group Eurofins Pharma Services LUX Holding, in a deal again expected to complete this fiscal year.

The company has already shed a variety of other non-core assets over the past few years, including a portfolio of old products in Japan, research operations at US subsidiary **Agensys Inc.**, and the global dermatology business to **Leo Pharma AS** in late 2015.

REFOCUSING UROLOGY

Strategic Plan 2018 sees net sales at the FY2017 level – around JPY1,300.3bn – by its end, reflecting the expected major generic challenges to Vesicare.

Taking center stage to help overcome the impact will be prostate cancer drug *Xtandi* (enzalutamide), for which the strategic aim is to expand indications to earlier line use from the fourth-line plus current label in metastatic castration-resistant disease.

Helped by increased penetration to urology specialists, Yasukawa said the goal is for high single-digit compound annual percentage growth for the drug over the period to the end of fiscal 2020 (March 2021), with peak global annual sales of JPY400-500bn ($3.65-4.57bn).

In the year to this March 31, the androgen receptor inhibitor sold JPY294.3bn globally, with strong growth across all regions. The Phase III EMBARK study to support use in non-metastatic, biochemical recurrence disease is "going well" as part of the strategy to support earlier stage use, a shift the CEO said would yield more targets patients that use the drug for longer.

Xtandi has also recently been filed in China, where Yasukawa said regulatory reforms should help its approval and growth prospects there.

Elsewhere in urology, mirabegron for overactive bladder (sold as *Betanis/Myrbetriq/Betmiga*) is seen growing in the low teens percentage under the new plan, helped by new combination use with Vesicare.

Fezolinetant, an NK3 receptor antagonist for menopause-related vasomotor symptoms in Phase II US trials, is seen as another key mid-term contributor, peaking at JPY200-300bn per annum.

Despite the planned closures, Yasukawa stressed an intention to reinforce Astellas' presence and launches in Japan, regardless of what he described as a "very tough" environment.

Key growth products there will be romosozumab for osteoporosis and peficitinib for rheumatoid arthritis, for which filings are planned this fiscal year.

MODAL MODEL

In common with some Japanese peers such as Chugai, Astellas is pursuing a treatment modality research model, based on non-therapeutic approaches such as antibodies, vaccines and cell/gene therapies, helped by well-characterized pathophysiology and the acquisition of innovative technology.

This is being divided under the new plan into key areas such as ophthalmology, cell therapies, muscular disorders, and immunology.

In the last of these areas, approaches involving novel immuno-oncology therapeutics such as checkpoint inhibitors and co-stimulatory agonists are being pursued for tumor types unresponsive to PD-1/PD-L1 blockers helped by the existing alliance with **Potenza Therapeutics Inc.**.

Yasukawa noted Astellas has also set up a specialist team to pursue "Rx+" initiatives in areas such as antibody combinations with medical technology such as radio-isotopes or nanomaterials, and digital devices to replace or add value to new treatments.

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From the editors of PharmAsia News

Remember When Provenge's Price Was Bold? Every New Cancer Drug In 2017 Cost $100,000 Or More

JESSICA MERRILL jessica.merrill@informa.com

A new report by the IQVIA Institute for Human Data Science highlights striking increases in cancer drug prices during the last five years: the median price of new oncology drugs in the US more than doubled between 2013 and 2017.

IQVIA found in its global oncology trends report released May 24 that the median annual price of new oncology brands launched in the US in 2017 was more than $160,000, up from $79,000 in 2013. Strikingly, no new cancer therapies had annual costs below $100,000 in 2017, while seven of 11 launches did in 2013, the report says.

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"As the cancer drugs have advanced from a clinical profile and a clinical endpoint perspective, we have also seen these list prices increase as well," IQVIA Institute Executive Director Murray Aitken said on a media call.

Most cancer drugs were used by relatively few patients, IQVIA said, with about 87% of drugs being used by fewer than 10,000 patients in 2017.

It was eight years ago in 2010 that **Dendreon Corp.** drew attention when it priced the prostate cancer immunotherapy *Provenge* (sipuleucel-T) at an annual price of $93,000 for a three-course treatment. But the growing acceptance of Provenge raised the price ceiling for new cancer drugs, and prices of $10,000 and higher per month became the new norm. By 2013, cancer drug manufacturers were continuing to push the limits.

IQVIA also pointed out that the introduction of some products with costs that far exceed median costs has become more common. The mean annual price of new brands in 2017 was $200,000, for example.

Despite the higher prices, IQVIA pointed out that the new drugs target significantly smaller, more focused subpopulations of patients. Most cancer drugs were used by relatively few people – about 87% of cancer medicines treated fewer than 10,000 patients in 2017.

"Generally, high costs correlate with lower numbers of patients," the IQVIA report says. "However, there are some notable exceptions where very effective treatments have patient populations of 10,000 to 50,000 and costs above $50,000 per year." The report cited 10 examples of well recognized blockbuster drugs: *Herceptin* (trastuzumab), *Velcade* (bortezomib), *Avastin* (bevacizumab), *Revlimid* (lenalidomide), *Perjeta* (pertuzumab), *Xtandi* (enzalutamide), *Imbruvica* (ibrutinib), *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab).

CANCER DRUG SPENDING IS BOOMING

US spending on cancer drugs has doubled since 2012, and reached $49.8bn in 2017, with more than 75% of the growth coming from the use of drugs launched in the last five years. The launch of PD-1/L1 inhibitors like **Merck & Co. Inc.**'s Keytruda, **Bristol-Myers Squibb Co.**'s Opdivo and others accounted for 20% of the growth.

Outside the US, oncology spending reached $60.6bn, representing an increase of 72.6% from 2012. Global spending on cancer medicines – both for therapeutic and supportive care – rose to $133bn in 2017, up from $96bn in 2013.

Spending on cancer medicines is heavily concentrated, with the top 35 drugs accounting for 80% of total spending. More than half of cancer drugs have less than $90m in sales. Those products account for only 2% of oncology spending as they are often older medicines that are available as generics. Of the cancer drugs available around the world, 80% generated less than $1bn and 72% generated less than $500m, according to IQVIA.

The growth trajectory is expected to continue, with the global market for oncology drugs expected to reach $200bn by 2022, averaging 10% to 13% annual growth over the next five years. US cancer drug spending is expected reach as much as $100bn by 2022, with growth averaging 12% to 15% each year.

Even as some industry observers have started to question whether pharmaceutical companies are over-invested in cancer R&D, the research trend shows little sign of slowing down.

IQVIA reported that the industry's cancer pipeline has reached a historic level with more than 700 molecules in development in 2017, up more than 60% versus a year ago. Immunotherapies are a particularly active area of R&D, with nearly 300 molecules involving 60 different mechanisms of action being evaluated in Phase I and Phase II clinical trials.

The most popular immuno-oncology mechanisms – CTLA-4, PD-1/L1 and chimeric antigen T-cell receptor (CAR-T) cell therapies – made up a large portion of emerging therapies, about one-third of Phase I and Phase II trials. CD3 modulators, such as Amgen's *Blincyto* (blinatumomab), made up 8% of Phase I and Phase II trials. Meanwhile, IDO/INDO inhibitors – once thought to be the next big IO breakthrough – made up 17% of Phase III/pre-registration trials. Recently, several disappointing trial readouts have dimmed the prospects for these drugs. *(Also see "A Wake For IDO: Bristol Ends Registrational Trials Of High-Priced Flexus Drug" - Scrip, 30 Apr, 2018.)*

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More Evidence Needed For Chiesi's Ultra Orphan Lamzede, Says NICE

FRANCESCA BRUCE francesca.bruce@informa.com

Chiesi could have its work cut out to persuade NICE, the health technology appraisal institute for England and Wales, that its enzyme replacement therapy *Lamzede* (velmanase alfa) is a cost-effective treatment for the ultra rare condition alpha-mannosidosis. The institute this week published draft guidance stating that it had too many doubts about the available evidence and the company's economic modelling.

Draft guidance published May 23 is based on recommendations from the highly specialised evaluation committee. The latter noted "important limitations" in the evidence available and said that the size and nature of the clinical benefits offered by the treatment over the short and long term were "highly uncertain," according to the evaluation consultation document.

For one thing, the evidence from two clinical trials showed that Lamzede was associated with statistically significant improvement in serum oligosaccharide levels. However, the committee was concerned that serum oligosaccharide levels was a surrogate outcome. It added that there appeared to be only a limited relationship between serum oligosaccharide levels and clinical outcomes in the rhLAMAN trials.

Among other things, there were also concerns that infection rates had not been collected as an efficacy outcome from the clinical trials. While the committee was able to conclude that the product appeared to have immunological benefits, it said the evidence was limited.

The company's economic modelling also failed to convince the committee, which expressed concern that the model was "based on expert opinion rather than clinical evidence." According to the evaluation consultation document, most parameters used to inform the model came either from an expert elicitation panel or from KOL interviews and not the clinical trials. This was because the clinical trials that generated the evidence did not capture clinically important aspects such as severe infections or the need for surgical invention. The committee concluded that "the extensive use of elicited data and expert opinion, and the lack of observed evidence to inform the model, were significant limitations in the economic analysis, and the magnitude and direction of any errors or bias were unknown."

It will remain committed to working with NICE and NHS England to find a solution that ensures eligible patients with alpha-mannosidosis can access velmanase alfa.

Lamzede's list price is £886.61 per 10mg vial and the estimated annual cost per patient is between £138,000 and £323,000. Chiesi did offer a patient access scheme in the form of a confidential discount, but this was not enough to offset the uncertainties in the evidence and economic modelling. The most plausible incremental cost-effectiveness ratio remains confidential but is "substantially higher than the range that can be considered an effective use of NHS resources for highly specialised technologies," said the evaluation consultation document.

THE QUEST FOR MORE EVIDENCE

That the evidence base for Lamzede is at present limited is unsurprising given that alpha-mannosidosis is a very rare condition, thought to affect around 30 people in the UK, while there have been approximately 200 cases reported worldwide, according to the company. Indeed, the therapy won EU approval under an exceptional circumstances mechanism that allows the assessment of treatments for extremely rare disorders for which bigger, more traditional clinical trials are unsuitable.

More evidence could be gathered to clear up the "substantial uncertainties" associated with the product through a managed access arrangement, according to the NICE evaluation consultation document. However, at present, Lamzede cannot be recommended within such an arrangement because it does not have the potential to be considered cost-effective, said the document.

Nevertheless, efforts to generate more data are underway, including two open-label follow-up studies in patients previously enrolled in development trials, and a compassionate care program in several EU countries. An international registry study is also planned for later in 2018, which will track existing and new patients across Europe for 15 years. In addition, a pediatric-only open-label study in patients aged less than six at start of treatment will be completed by 2020.

A disappointed Chiesi said it will "remain committed to working with NICE and NHS England to find a solution that ensures eligible patients with alpha-mannosidosis can access velmanase alfa." However, it declined to comment any further on what course of action it might take.

The Italian firm has set its sights on becoming a leader in rare diseases and inked two deals in 2017. In the first it bought **Horizon Pharma PLC**'s European subsidiary, and secured the Europe, Middle East and Africa rights to two approved drugs - *Procysbi* (cysteamine bitartrate) to treat nephropathic cystinosis, a rare metabolic disorder and *Quinsair* (inhaled levofloxacin) for the management of chronic pulmonary infections caused by *Pseudomonas aeruginosa* in adults with cystic fibrosis.

In the other deal, Chiesi signed a collaboration with **Protalix BioTherapeutics Inc.** for the development and commercialization of PRX-102 (pegunigalsidase alfa), a chemically modified version of the recombinant protein alpha-galactosidase for the treatment of Fabry disease.

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Former Gilead CSO Bischofberger Lands At Kronos As C-Suite Moves To Start-Ups Continue

MANDY JACKSON mandy.jackson@informausa.com

Former **Gilead Sciences Inc.** Executive Vice President for Research and Development and Chief Scientific Officer Norbert Bischofberger left the company just as its oncology portfolio was gaining traction to run a start-up called **Kronos Bio Inc.**, which is developing drugs against difficult cancer targets.

Kronos announced on May 23 that the nearly 30-year Gilead veteran was recruited as its president and CEO. The Cambridge, Mass.-based company has raised $18m in seed funding, some of it from Bischofberger and his connections. He is among a growing group of executives moving from the C-suite at public big pharma and large biotech companies to the entrepreneurial arena of start-ups and venture capital financing.

Bischofberger, with Gilead almost since its inception when it had 25 employees, said in the Kronos announcement that he is "excited to apply the wisdom and experience I've gained and return to my roots in early-stage biotechnology."

The new company also gives Bischofberger a chance to build a cancer-focused firm, whereas oncology is a small part of Gilead's portfolio dominated by multibillion-dollar HIV and hepatitis C franchises. The executive left Gilead just as it was beginning to gain traction in oncology following the $11.9bn acquisition of chimeric antigen receptor T-cell (CAR-T) specialist **Kite Pharma Inc.** in 2017. *(Also see "What's Gilead Getting From Kite For Nearly $12bn?" - Scrip, 29 Aug, 2017.)*

Kronos' $18m seed round was led by several investors associated with Gilead and Kite, including Bischofberger and Gilead Chairman John Martin. Other investors include Omega Funds, the new venture capital firm Vida Ventures LLC headed by former Kite CEO Arie Belldegrun, and his wife Rebecka Belldegrun's VC firm BellCo Capital. Omega's Otello Stampacchia, Bischofberger, Martin and both Belldegruns serve on the Kronos board of directors; Arie Belldegrun is the chairman.

The Kronos platform comes from the

Norbert Bischofberger

lab of Scientific Founder Angela Koehler, an assistant professor at the Koch Institute for Integrative Cancer Research at the **Massachusetts Institute of Technology** (MIT), who has worked for more than a decade on high-throughput screening strategies for chemical modulators of transcription factors and other elusive oncology targets.

Bischofberger describes the company's platform as focused on "solutions, not challenges." It combines small molecule microarrays with biological assay development expertise to enable high-throughput screens of chemical libraries against targeted proteins in a context that's more relevant to specific types of cancer. The goal is rapid discovery of unique ligands for use in novel modulators or degraders of targets previously viewed as undrugable.

Kronos has two programs in preclinical development targeting the MYC family of transcription factors, which are dysregulated in many types of cancer, and the androgen receptor in prostate cancer.

ENTREPRENEURIAL C-SUITE MOVERS AND SHAKERS

The new company can boast what many start-ups would love to have at their outset – deep-pocketed investors and highly experienced leadership with decades of knowledge about not only drug development and business development, but also commercialization of new therapies.

Other pharma/biotech top-level executives recently leaving corporate life behind to immerse themselves in entrepreneurial endeavors and novel science include former **Genzyme Corp.** CEO David Meeker, who headed that organization even after its acquisition by **Sanofi**. He launched **KSQ Therapeutics** last year with $76m in Series A venture capital. *(Also see "KSQ Comes Out Of Stealth Mode With $76m And Meeker As CEO" - Scrip, 2 Oct, 2017.)*

MORE NEW BIOTECHS

Meanwhile, **Vir Biotechnology Inc.** launched at the start of 2017 with $150m in initial funding and a focus on infectious diseases with former **Biogen** CEO George Scangos at the helm. Around the same time, the venture capital firm Flagship Pioneering recruited former Novartis Pharmaceuticals CEO David Epstein as an executive partner, which followed the 2016 recruitment of retired **Merck & Co. Inc.** Chief Medical Officer Michael Rosenblatt as Flagship's CMO.

Before that, ousted Sanofi CEO Christopher Viehbacher joined the $2bn investment firm Gurnet Point Capital and launched **Boston Pharmaceuticals Inc.** with $600m in 2015 to acquire early clinical-stage drug candidates, de-risk the assets, and then license or sell them to larger pharma companies. *(Also see "Viehbacher On Boston Pharmaceuticals: A New Model To De-Risk Drugs" - Scrip, 20 Nov, 2015.)*

Arie Belldegrun took a path similar to Viehbacher's after Gilead acquired Kite, launching both Vida Ventures and the CAR-T-focused start-up

Allogene Therapeutics Inc. earlier this year. *(Also see "'We Jumped' At Opportunity To Take On Pfizer's CAR-T Program, Allogene's Chang Says" - Scrip, 4 Apr, 2018.)*

And after **Amgen Inc.** acquired **Onyx Pharmaceuticals Inc.** for $10bn in 2013, Onyx CEO Tony Coles launched **Yumanity Therapeutics** focused on neurodegenerative diseases with $45m in Series A funding.

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Esperion Posts Positive Phase III Bempedoic Acid Results, But Future Fixed-Dose Data Are Key

MANDY JACKSON mandy.jackson@informausa.com

Esperion Therapeutics Inc.'s latest Phase III results for bempedoic acid in statin-intolerant patients with atherosclerotic cardiovascular disease (ASCVD) or at high risk for ASCVD met the LDL cholesterol-lowering primary endpoint and, importantly, didn't raise any new safety questions.

However, the data that may be most important for the oral therapy's commercial future aren't expected until August, when Esperion plans to disclose the first Phase III results for its fixed-dose combination (FDC) of bempedoic acid and **Merck & Co. Inc.**'s now generic drug *Zetia* (ezetimibe). The FDC may be the company's best shot at sales success, since bempedoic acid is not as effective as a monotherapy or an add-on as the injectable PCSK9 inhibitors, which continue to lower their prices to gain access to patients.

Esperion reported results on May 23 from the Phase III clinical trial known as Study 3, which enrolled 345 patients who were randomized 2:1 to treatment with bempedoic acid or placebo. The primary endpoint was LDL-cholesterol (LDL-C) lowering at 12 weeks, while secondary endpoints included LDL-C lowering at 24 weeks, safety and tolerability, and effects on other risk factors, including high-sensitivity C-reactive protein (hsCRP), a marker of inflammation associated with cardiovascular disease.

Bempedoic acid met the Study 3 primary endpoint with a 23% reduction in LDL-C versus a 1% decrease in the placebo group at 12 weeks in the intent-to-treat population ($p<0.001$). LDL-C lowering was 26% for patients on bempedoic acid at both week 12 and week 24 versus 2% in the study's placebo arm. Also, hsCRP was reduced by 25% for patients treated with bempedoic acid versus a 3% increase for placebo-treated patients ($p<0.001$).

Esperion described the results as consistent with previously reported data for bempedoic acid in statin-intolerant patients. The company reported data from Study 4 in statin-intolerant patients with or at high risk of ASCVD – a trial similar to Study 3 – in March. *(Also see "Esperion's Oral Bempedoic Acid Passes First Phase III Cholesterol Test" - Scrip, 7 Mar, 2018.)*

ENOUGH BENEFIT TO BEAT INJECTABLE COMPETITION?

Datamonitor Healthcare senior analyst Jack Allen said the efficacy results were essentially in line with expectations, but he questioned bempedoic acid's ability to compete as a standalone therapy in the evolving market for cholesterol-lowering drugs.

As the makers of PCSK9 inhibitors – **Amgen Inc.** with *Repatha* (evolocumab) and **Sanofi/Regeneron Pharmaceuticals Inc.** with *Praluent* (alirocumab) – continue to lower the biologics' prices so that US payers will cover the cost of their products, Allen said bempedoic acid's potential market is likely to shrink.

Sanofi/Regeneron revealed a deal with **Express Scripts Holding Co.** in early May that will bring Praluent's cost down from a list price of $14,600 per year to the low end of a price range outlined by the Institute of Clinical and Economic Review – $4,500 to $8,000. Esperion has suggested a list price of about $3,300 to $3,600 per year for bempedoic acid.

Allen noted that the anti-PCSK9 therapies have been safe and shown much higher efficacy than bempedoic acid, so if they are priced similarly to the Esperion drug then he would expect physicians to prescribe Repatha or Praluent first.

However, he also pointed out that the fixed-dose combination of bempedoic acid and ezetimibe should improve the drug's efficacy, so the oral combo pill could steal some market share from PCSK9 inhibitors if data from another Phase III study due in August – an evaluation of the FDC in 350 patients with or at high risk of ASCVD on maximally tolerated statins – show acceptable safety and improved efficacy.

"As a result, I would expect the FDC to account for most of the bempedoic acid franchise uptake, though the franchise as a whole faces headwinds as PCSK9 prices continue to drop," Allen said.

PCSK9 inhibitors have shown LDL-C lowering in the range of 50% to 60% in populations also treated in Esperion's trials – about two times the cholesterol lowering provided by bempedoic acid monotherapy, which makes the biologics attractive clinically despite being injectable administration.

Needham analyst Chad Messer suggested in a May 23 note that bempedoic acid has a good chance of at least matching the PCSK9 inhibitors' LDL-C lowering based on Phase II results for the drug in combination with ezetimibe.

"An earlier Phase II study of patients with hypercholesterolemia [treated with the] combination of ezetimibe and bempedoic acid showed LDL-C reductions from baseline of up to 48%. The current combo study is evaluating sicker patients with ongoing ASCVD," Messer wrote.

SAFETY ALSO A NEEDED DIFFERENTIATOR

The anti-PCSK9 drugs also have proven to be fairly safe and have the benefit of cardiovascular outcomes trial (CVOT) data showing some improvement in cardiovascular outcomes, so safety is an important factor for bempedoic acid's marketability as well.

Results from Esperion's large safety trial known as Study 1, which were reported on May 2, shocked investors who worried that the company would not be able to submit bempedoic acid for US and EU approvals as planned during the first half of 2019 before completion of a CVOT. There were 15 deaths in Study 1, including 13 in the bempedoic acid arm of the trial.

Esperion's stock fell 35% at that time to $45.75 per share and has not recovered in the ensuing weeks. It dropped another 3.6% to close at $38.32 on May 22 after the top-line Study 3 results were released along with cumulative safety data from all of bempedoic acid's Phase II and III studies to date.

The company described bempedoic acid as safe and well-tolerated and noted that there were no deaths in the drug and placebo arms of Study 3. Muscle-related adverse events – side effects are associ-

ated with patient reports of statin intolerance – were lower in the bempedoic acid group. Esperion said "there were no clinically relevant differences in the occurrence of adverse events (AEs) and no differences between the treatment group and the placebo group in discontinuations due to muscle-related AEs."

Rates of serious adverse events (SAEs) in Study 3 were 6% among bempedoic acid-treated patients versus 3.6% in the placebo group, but no SAEs were determined to be related to the drug. Treatment discontinuation rates due to AEs were 18.4% and 11.7% for bempedoic acid and placebo, respectively, with no particular side effect pinpointed as the reason for patients dropping out of either arm of the study. The rate of elevations in liver function tests (LFTs) was 0.43% versus 0% for placebo, which Esperion said is consistent with the 0.56% rate observed across bempedoic acid (BA) studies to date and similar to LFT elevation rates for approved oral therapies, including statins and ezetimibe.

"We look for sentiment to gradually improve with continued delivery of what we consider datasets supporting [bempedoic acid's] approval and look to key remaining Phase III readouts in 3Q 2018 (including the 52-week Study 2) to fully flesh out BA's clinical profile," Credit Suisse analyst Martin Auster said in a May 23 note.

CAN CUMULATIVE RESULTS EASE ANXIETY?

Esperion also reported cumulative Phase II and III results from more than 4,000 patients, including more than 2,600 treated with bempedoic acid, which show LDL-C lowering of 20%-24% for patients treated with bempedoic acid on background statin therapy and 23%-30% when statins weren't administered. Also, hsCRP was reduced by 22% to 40%, across these trials.

Cumulatively, Esperion said results to date show "no clinically relevant differences between the bempedoic acid and placebo groups in the occurrence of AEs." Adverse event rates and discontinuation rates due to AEs are 67.8% and 9.5% for bempedoic acid, and 66.1% and 6.9% for placebo. SAE rates were 9.2% for bempedoic acid and 8.9% for placebo, with fatal adverse event rates of 0.5% and 0.2%, respectively. None of the deaths were determined to be related to bempedoic acid or its comparators.

"Today's largely positive Study 3 results should help add incremental confidence in the overall efficacy and safety of BA when looking at the totality of data to date," Jefferies analyst Michael Yee wrote in a May 23 note. "While some may question SAEs seen today, no particular event was higher than 1% and in context of pooled database of 2600+ patients on BA in Phase II/III trials, the safety profile of BA looks good. However, Study 2 in September will hopefully add to the balanced cumulative data."

Study 2 is Esperion's second Phase III trial enrolling 750 patients with ASCVD on maximally tolerated statin therapy – the same population as the troubling Study 1 – who were followed for one year.

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Novo Nordisk Boosts Specialty R&D With Kidney Disease Deal

JOHN DAVIS john.davis@informa.com

Novo Nordisk AS showed its interest in acquiring external research assets by its failed bid for **Ablynx NV** and that company's blood disorders lead program, earlier this year and, subsequently, the Danish biopharma has not strayed far from its best-selling diabetes and hemophilia sectors when forging new deals, including its latest collaboration, with US biotech **Epigen Biosciences**.

In a deal worth up to $200m in upfront and milestones to be paid to Epigen, Novo Nordisk has licensed the San Diego, CA-based biotech's LPA1 receptor antagonist, EPGN696, for development in diabetic and chronic kidney disease and other chronic diseases associated with metabolic syndrome. Further, Epigen will also be eligible for tiered royalties and milestones on sales, the companies announced May 23.

EPGN696 appears to be close to Novo Nordisk's current research focus on metabolic diseases that includes obesity as well as diabetes. EPGN696 is an antagonist at the lysophosphatidic acid receptor-1 (LPA1) that is thought to be involved in cell signalling and proliferation, including the formation of excess fibrous connective tissue, in the kidneys and other organs. In preclinical studies, EPGN696 has been found to be orally available and safe and effective in rodent models of kidney disease, by targeting fibrosis, inflammation and growth factor responses, the companies said.

There are a number of subtypes of LSA receptors, that have been implicated in various physiological processes, and the pharmaceutical industry appears to be at an early stage in evaluating candidate products acting through LSA receptor-mediated processes.

According to Informa's Biomedtracker database, **Apollo Endosurgery Inc.** has lpathomab, a monoclonal antibody, in Phase I studies for neuropathic pain, and preclinical studies for diabetic peripheral neuropathy and spinal cord injury, while **Roche** has ITMN-10534 in preclinical studies for idiopathic pulmonary fibrosis.

But the pressure is on to broaden the Danish company's specialty portfolio, particularly because of the pricing squeeze on its marketed insulin products in the US. Novo Nordisk is on the look-out for an acquisition in the rare diseases space, and on assets in diseases adjacent to diabetes, including conditions that affect the liver, kidneys and cardiovascular system, its CEO said earlier this year.

Earlier this month, Novo Nordisk said it had achieved GMP-compliant human embryonic stem cell production as part of an ongoing collaboration with the University of California in San Francisco that might be used in regenerative medicine therapies, including potential in the treatment of diabetes, and in other chronic diseases, such as Parkinson's disease.

And earlier this year, Novo Nordisk strengthened its blood disorders research portfolio by licensing a potential sickle cell compound, EP101, from **EpiDestiny Inc.**, that is moving into Phase II studies.

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BioMarin, Spark Hemophilia Gene Therapies Progress As Accelerated Approval Favors Their Indications

MANDY JACKSON mandy.jackson@informausa.com

It remains unclear how long the effects of hemophilia gene therapies from **BioMarin Pharmaceutical Inc.** and **Spark Therapeutics Inc.** will last, but the US FDA plans to release guidance documents soon that will recommend putting gene therapies for hemophilia on course for accelerated approval.

New Phase I/II data for BioMarin's valoctocogene roxaparvovec (BMN 270) in hemophilia A and Phase I/II data for SPK-9001 in hemophilia B from Spark and partner **Pfizer Inc.** were presented at the World Federation of Hemophilia (WFH) World Congress in Glasgow, Scotland on May 22. Both studies showed that patients generated enough of their own clotting factor to eliminate the need for factor infusions almost entirely, although the duration of effect for BioMarin's gene therapy is in question.

Even so, FDA Commissioner Scott Gottlieb said during a May 22 briefing with Alliance for Regenerative Medicine (ARM) members in Washington, D.C. that factor production may be enough for accelerated approval with efficacy confirmed post-approval.

FACTOR PRODUCTION AT BENEFICIAL LEVELS

Both BioMarin's and Spark's lead gene therapy candidates for hemophilia have shown production of clotting factors at beneficial levels in patients. However, BioMarin's stock fell slightly after the company's new data showed that factor levels in the treated patients have declined since a prior update, raising questions about the durability of valoctocogene roxaparvovec's therapeutic effect.

BioMarin said in a same-day conference call that it believes factor levels have plateaued in those patients, given the results the company saw in primates during its preclinical research, but its stock closed down 2% at $87.61 per share on May 22. However, the stock fell as low as $84.02 in morning trading before recovering by more than $2 in the afternoon following Gottlieb's ARM briefing.

BioMarin previously reported results for 10 patients treated with valoctocogene roxaparvovec at the American Society of Hematology (ASH) meeting in December. *(Also see "Spark Plots Rebound For Hemophilia A Gene Therapy, As Rival BioMarin Surges" - Scrip, 12 Dec, 2017.)* New data from the company's ongoing open-label Phase I/II study at the WFH meeting concerned 15 patients treated with a 4e13 vg/kg dose of the gene therapy for one year or a 6e13 vg/kg dose for two years with April 16 as the data cutoff.

BioMarin said there were continued and substantial reductions in bleeding that would require factor VIII (FVIII) infusions, no spontaneous bleeds and bleeding in joints was eliminated in the second year for patients who received the higher dose. The improvement in quality of life as measured by the six-domain Haemo-QoL-A instrument was up to three times the 5.2-point improvement that's considered to be clinically important.

No patients developed FVIII inhibitors, but there were two serious adverse events (SAEs), including a hospitalization for observation due to Grade 2 pyrexia with myalgia and headache that resolved within 24 hours of infusion with valoctocogene roxaparvovec. The other SAE was not related to the gene therapy, but was associated with a planned knee replacement surgery to treat prior hemophilic arthropathy.

Mean FVIII activity level in the 6e13 vg/kg cohort was within the normal range at 59% and the median was near normal at 49%. Analysts noted that the mean was lower than the 90% FVIII level reported at 18 months of treatment.

"Based on animal model data, management believes that the peak-to-trough levels for the FVIII expression is similar in humans to animals, suggesting a plateau. We believe the overall data is strong, reflecting significant declines in FVIII use and setting up the program well for superiority," Morgan Stanley analyst Matthew Harrison wrote in a May 22 note.

BioMarin revealed alongside its new Phase I/II results for valoctocogene roxaparvovec that it has increased the size of its ongoing Phase III study known as GENEr8-1 from 40 hemophilia A patients to 130 patients, which should power the study to show superiority of the 6e13 vg/kg dose to standard of care FVIII infusions administered for prophylaxis. The comparator in the study will be patients' own treatment history on FVIII prophylaxis.

Enrollment in GENEr8-1 is expected to be complete in the first quarter of 2019 versus BioMarin's prior guidance of the second half of 2018. Enrollment in the 40-patient Phase III GENEr8-2 study testing the lower 4e13 vg/kg dose is expected to conclude in the second or third quarter of 2019.

"While some investors may be disappointed in the extending of timelines, we see the superiority study as the right thing to do which should support the commercial potential," Harrison wrote.

SPARK FOLLOWS BIOMARIN

Spark's own hemophilia A gene therapy SPK-8011 is behind BioMarin's, still testing the candidate in a handful of patients with an update expected later this year. However, the company said on May 22 that it has concluded enrollment in the Phase I/II study for SPK-9001 in hemophilia B and will complete the transition of the program to Pfizer this summer.

Spark and Pfizer agreed to collaborate on the development of a factor IX (FIX)

Phase I/II Results For Valoctocogene Roxaparvovec

	4e13 vg/kg In Year One	6e13 vg/kg In Year Two
Reduction in annualized bleed rate (ABR)	92%	97%
Percentage of patients with zero bleeds requiring FVIII infusion	83% versus 17% for the year before treatment	71% during Year 1 and 86% in Year 2 versus 14% for the year before treatment
Reduction in mean FVIII usage	98%	96%
Quality of life improvement via Haemo-QoL-A	3.8-point mean improvement from baseline	Up to a 17.3-point mean gain

gene therapy program for hemophilia B in December 2014. The agreement put Spark in charge of the program through Phase I/II with Pfizer taking responsibility for pivotal studies, regulatory activities and global commercialization.

"While no timelines have been provided for the Phase III study, we believe Pfizer's global network and trial expertise will facilitate rapid execution; we project a commercial launch in 2021," Credit Suisse analyst Martin Auster said in a May 22 note.

The Phase I/II data for SPK-9001 at the WFH meeting on May 22 also updated results previously presented at ASH in December. Spark said all 15 patients treated with SPK-9001 to date have discontinued routine FIX infusions with no serious adverse events, no thrombotic events and no FIX inhibitors detected as of the May 7 data cutoff. Thirteen of the 15 had at least 12 weeks of follow-up after infusion with SPK-9001.

The average bleed rate was reduced by 98% after week 4 (97% from baseline). The annual rate of bleeds per patient was reduced to 0.2 versus 8.9 bleeds per year before SPK-9001 administration.

The annual infusion rate was cut by 99% after week four and compared to baseline. The annual rate was 0.9 infusions per patient versus 57.2 infusions per year before SPK-9001. Six patients received a FIX infusion after treatment with the gene therapy, including two for spontaneous bleeds, two prior to surgery, one at the end of the study and one for prophylaxis after a traumatic non-bleeding event.

Steady-state FIX activity was 14.3% to 76.8% from week 12 through week 52 for the first 10 patients in the Phase I/II study and range from 38.1% to 54.5% for three patients who reached at least 12 weeks of follow-up after infusion with SPK-9001 produced in Spark's enhanced manufacturing process.

"In our view, these results would suggest that Spark/Pfizer new manufacturing process at a minimum provides equivalent results compared to product produced using the original process, which should alleviate any investor concerns around the product for the Phase III trial," Jefferies analyst Michael Yee wrote in a May 22 note. "While still early and the patient number is low, these results could also indicate that the new process could potentially be less variable than the original manufacturing process – which would be a surprising positive as even more consistent results could alleviate one of the chief concerns that we have heard from [key opinion leaders (KOLs)], which is consistency."

FACTOR PRODUCTION KEY TO ACCELERATED APPROVAL

FDA Commissioner Gottlieb has said that about 20% of the agency's review of an application for a typical drug is manufacturing while the rest is safety and efficacy, but noted that the opposite is true for gene therapies, given their complex manufacturing processes.

And he indicated at a conference on May 10 that the FDA would release guidance documents related to the manufacturing and development of gene therapies in six weeks, which would be around mid- to late June. Earlier in May, he said accelerated approval endpoints for gene therapies targeting specific diseases, such as hemophilia, would be included in the guidance.

But Gottlieb confirmed during the May 22 ARM briefing that hemophilia is indeed the first indication for which the FDA intends to consider accelerated approval of gene therapies. "The first therapeutic area we'll focus on is hemophilia, where factor production may be sufficient in some cases as a surrogate measure of benefit where a gene therapy product can potentially normalize factor production," he said. "In these settings, the demonstration of a reduction in bleeding rates could be confirmed post approval, as we continue to study a product's long-term safety and durability." The FDA's fiscal year 2019 budget request asks for funds to support increased collection of post-market data for new drugs, Gottlieb added.

Spark, whose stock traded as low as $72.65 earlier in the day, also rallied after the commissioner's comments. The company ended May 22 at $74.83 per share, a 2.4% gain versus the prior day.

Both Spark's SPK-9001 and BioMarin's valoctocogene roxaparvovec have breakthrough therapy designations from the FDA and Priority Medicines (PRIME) designations from the European Medicines Agency for the treatment of hemophilia B and hemophilia A, respectively.

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Cipla's Respiratory Ambition

ANJU GHANGURDE anju.ghangurde@informa.com

Cipla Ltd., which has been expanding its respiratory franchise globally, has indicated that it is revving up in the segment in the US, a market where the Indian firm has traditionally derived a smaller proportion of its overall revenues compared with some large Indian peers.

The Indian company may be lagging some frontliners for a generic version of *Advair* (fluticasone/salmeterol) in the US but management commentary provided some insights around why it may still be an interesting play. Cipla has initiated clinical trials for generic version of Advair in the US and "groundwork" for two more trials in the "near future" is also underway.

Cipla's managing director and global CEO, Umang Vohra, said that the company remained committed towards establishing a regulated market respiratory franchise and had achieved "significant milestones" during the year.

"We are targeting one sizeable respiratory inhalation launch in the US every year, starting next year with albuterol," Vohra said on a post results earnings call May 22.

To an analyst's query on any potential challenges around the company's albuterol, in the backdrop of **Perrigo Co. PLC**'s recent Complete Response Letter (CRL) from the US FDA, Vohra said he doesn't see any "challenges of the clinical study and what we saw in the study". He referred, though, to "some regular correspondence" that needs to be answered to the FDA.

"We are quite confident that we should be able to do it in due course. So, nothing which we believe will stop us right now."

The US accounted for 17% of Cipla's FY2017-18 revenues but Cipla previously indicated that it expects the US contribution to revenues to go up to around 30% in FY2021-22.

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

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

Selected clinical trial developments for the week 18–24 May 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Sanofi/Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilimub)	asthma	LIBERTY ASTHMA QUEST, VENTURE; *NEJM*, May 21, 2018.
AstraZeneca PLC	tralokinumab	asthma	STRATOS 1, 2; *The Lancet Respiratory Medicine*, May 20, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Esperion Therapeutics Inc.	bempedoic acid	lipid lowering in statin intolerant patients	Study 3; positive top-line results.
Nabriva Therapeutics PLC	lefamulin, oral	community-acquired pneumonia	LEAP-2; positive results.
AbbVie Inc./Janssen Biotech Inc.	*Imbruvica* (ibrutinib) plus *Gazyva* (obinutuzumab)	chronic lymphocytic leukemia, first-line	iLLUMINATE; met primary PFS endpoint.
GlaxoSmithKline PLC	*Nucala* (mepolizumab)	asthma, severe eosinophilic	COLUMBA; long-term safety and efficacy supported.
UroGen Pharma Ltd.	*MitoGel* (mitomycin)	urothelial cancer, upper tract	OLYMPUS; durable complete responses.
Trevena Inc.	oliceridine	acute pain following colorectal surgery	Well tolerated in open label safety study.
Avenue Therapeutics Inc.	iv tramadol	pain following surgery	Effective and well tolerated.
UPDATED PHASE III RESULTS			
Merck & Co. Inc.	*Keytruda* (pembrolizumab)	squamous non-small cell lung cancer (NSCLC)	KeyNote-407; PFS and overall survival improved.
Sesen Bio Inc.	*Vicinium* (antibody drug conjugate)	invasive bladder cancer	VISTA; effective and well tolerated.
Roche	*Hemlibra* (emicizumab-kxwh)	hemophilia A	HAVEN 3, 4; prevented bleeding.
Shire PLC	*Vonvendi* (von Willebrand factor)	von Willebrand disease in surgical patients	Effective and well tolerated.
Shire PLC	*Natpara* (rhPTH(1-84))	hypoparathyroidism	RACE; well tolerated and effective in five-year data.
AstraZeneca PLC	*Bevespi Aerosphere* (glycopyrrolate/formoterol fumarate)	chronic obstructive pulmonary disease	PINNACLE-4; improved lung function.
Circassia Pharmaceuticals PLC	*Duaklir Pressair* (aclidinium/ formoterol)	chronic obstructive pulmonary disease	AMPLIFY; improved symptoms.
AstraZeneca PLC	*Fasrena* (benralizumab)	severe asthma	ZONDA; reduced oral steroids, improved lung function.
PHASE III ANNOUNCED			
Otsuka Holdings Co. Ltd./ Lundbeck Inc.	*Rexulti* (brexpiprazole)	agitation associated with Alzheimer's disease	A 12-week study.
MyoKardia Inc.	mavacamten	cardiomyopathies	EXPLORER-HCM.

Source: Biomedtracker

Phase III Beckons For A Short-Course Seasonal Allergic Rhinitis Jab

JOHN DAVIS john.davis@informa.com

Considering the setbacks suffered by allergy product developers over the past several years, **Allergy Therapeutics PLC** executives most likely gave a sigh of relief when a new Phase II dose-ranging study with its candidate grass allergy product concluded with positive top-line results.

The study, G205, established a "highly statistically significant" dose-response relationship for its grass-modified allergen tyrosine absorbed (MATA) monophosphoryl lipid A (MPL) candidate for preventing grass-pollen induced seasonal allergic rhinitis, and a dose to use in a forthcoming Phase III study was established, the company announced on May 21.

Worthing, UK-based Allergy Therapeutics reported the study met its primary endpoint of establishing a dose response relationship ($p<0.0001$), all dosing regimens were safe and well tolerated, and patient symptoms were significantly improved compared with placebo ($p<0.01$).

Treatment with the allergic rhinitis product consists of six weekly subcutaneous injections, but adherence was "excellent", with more than 95% of patients receiving the target cumulative dose, the company said. Increases in immunoglobulin were seen that correlated with the observed dose-responses.

"The results are great news, with every dose investigated being efficacious and well tolerated," said company CSO, Murray Skinner, in an interview. "The data backs up the Phase II PQ Birch studies which allowed us to find a safe and efficacious dose which is now being used in our current PQ Birch Phase III study," he added.

The grass allergy product results reported on May 21 contrast with those from a previous Phase II study, reported back in 2016, that produced inconclusive results, possibly because it used a mobile environmental exposure chamber. This time around a mobile chamber was not used, and the Phase II study evaluated changes in the total symptom score (TSS) following a conjunctival provocation test (CPT), in 447 European patients treated with either four different doses or placebo.

2016 also saw disappointing news from another allergy product developer, **Circassia Pharmaceuticals PLC**, whose cat allergy product, *Cat-SPIRE*, failed in a pivotal Phase III study, making investors cautious about the entire allergy sector.

Allergy Therapeutics's candidate grass allergy product is virtually identical to its short-course subcutaneous grass allergy product, *Pollinex Quattro*, which is available in the EU on a "named patient" basis. Obtaining marketing approvals for its allergy products would allow Allergy Therapeutics to broaden its commercial activities, as well as satisfying the demands of regulators, which are keen to assess the benefits and adverse effects of all named patient allergy products currently available in the marketplace in a systematic way.

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Russell Greig has been appointed chairman of French biotech, **Horama**, succeeding ***Thierry Laugel***. Greig worked at GlaxoSmithKline for three decades, including as president of the corporate venture group, SR One, and president of GlaxoSmithKline's Pharmaceuticals international from 2003 to 2008. Currently, Greig is also chairman of Ablynx, AM Pharma, Mint Solutions, eTheRNA and Sanifit. Horama is developing gene therapies for the treatment of rare, inherited retinal diseases, based on recombinant adeno-associated virus vectors.

The Leiden, Netherlands-based immune-oncology firm, **ISA Pharmaceuticals BV**, has promoted ***Gerben Moolhuizen*** from chief business officer to CEO, effective June 1, 2018, taking over from ***Ronald Loggers***, who has been CEO since 2013. Before ISA Pharmaceuticals, Moolhuizen was general manager at OctoPlus BV. ISA Pharmaceuticals's lead product is ISA101, that consists of 13 synthetic long peptides (25-35 amino acids) derived from the E6 and E7 oncogenic proteins of the HPV16 virus, and has completed an early-stage clinical study in vulvar intra-epithelial neoplasia.

The US biotech, **Calidi Biotherapeutics Inc.** (formerly Stemimmune Inc.) has appointed ***Allan Camaisa*** as CEO. The San Diego, CA-based company is developing the use of oncolytic virus for the treatment of cancer, including a cell-based system to deliver virus direct to tumors; US clinical studies with a potential prostate cancer product are expected to start later this year.

Samuel Saks has joined the US peptide-cased drug developer, **Protagonist Therapeutics**, as chief development officer, to provide strategic oversight to the company's R&D program. Saks was chief development officer and a board member at Auspex Pharmaceuticals before its acquisition by Teva Pharmaceuticals, and was a co-founder of Jazz Pharmaceuticals, where he served as CEO for six years. He is currently on the board of PDL BioPharma, Tonix Pharmaceuticals, Velocity Pharmaceutical Development and NuMedii. Protagonist has an interleukin-23 blocker, PTG-200, in Phase I to support a Phase II study in Crohn's disease..

Curis Inc, the Lexington, Mass.-developer of cancer therapies, has appointed ***Robert Martell*** as head of R&D., to manage Curis's clinical development and research efforts; Martell will step down from his Curis board duties effective June 1, 2018. Martell is a practicing oncologist and an associate professor at Tufts University School of Medicine, and previously served as chief medical officer at Tesaro and MethylGene. Curis's lead product, fimepinostat, is being evaluated in patients with lymphomas and solid tumors. ***David Tuck***, Curis's former CMO, is retiring from the company to return to academic clinical research.

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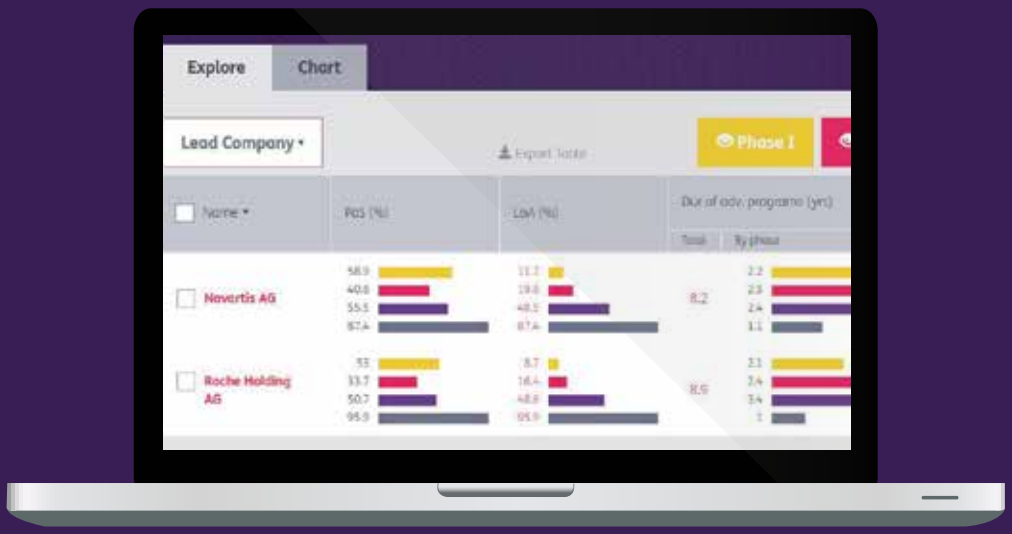

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