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Novartis' CAR-T Poised For The Market After Adcomm Success

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The FDA's Oncologic Drugs Advisory Committee recommended the FDA approve **Novartis AG**'s tisagenlecleucel (CTL019) on July 12, all but guaranteeing the drug will be the first chimeric antigen receptor T cell (CAR-T) therapy to reach the market. The focus now for Novartis and investors will be on how the company will turn its CAR-T platform into a commercial success story.

Assuming approval, the company will initially focus distribution on a few dozen treatment centers, to address safety and provider training issues. But the company also believes it can reduce production time by more than 80%, despite the complicated manufacturing process involved.

ODAC voted 10-0 in favor of the drug's approval for pediatric leukemia after a full day panel review that many in the industry hailed as historic given the innovative nature of the treatment, a living drug developed by extracting patients' cells, reengineering them to target CD19 to fight cancer and reinfusing them back into the patient.

After voting, reviewers' comments ranged from "the clinical responses are remarkable" to "the most exciting thing I've seen in my lifetime," while acknowledging the long-term risks remain unknown. Even some of Novartis' competitors applauded the outcome as a major step forward for the cancer treatment technology.

Despite impressive efficacy, the FDA's concerns with CLT019 and CAR-T therapies generally are around manufacturing, given the novelty of the manufacturing process and variability, and safety, particularly the risk of cytokine release syndrome, which has led to deaths in some patients. *(Also see "Novartis' CAR-T Therapy Faces Quality, Safety Concerns At FDA Advisory Panel" Pink Sheet, 10 Jul, 2017.)*

In the end, however, the efficacy seen following treatment with CTL019 in young patients who have little to no treatment options outweighed the panel's concerns. The positive recommendation is for the treatment of pediatric and young adult patients ages three to 25 years old with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

UNMET NEED AND PERSONAL STORIES INSPIRE VOTE

Children's cancer specialist Stephen Hunger of Children's Hospital of Philadelphia summed up the need for CAR-T therapy for young ALL patients who relapse, about 15% of patients.

"The options for these patients are quite limited," he told the panel. "Standard chemotherapy and hematopoietic stem cell transplant have limited efficacy. Patients who relapse post-transplant have a two-year overall survival rate of 15%."

A mother, Amy Kappen, spoke about her five-year old daughter Sophia, who was given CTL019 and experienced a "miraculous change" and saw the disease burden in her bone marrow drop from 98% to less than 1% in 28 days. But Sophia received the drug too late, after her disease had mutated. "CAR-T therapy did what it was intended to do for her marrow, but the mutation of her disease was

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In The Blood
Convenience is king for hemophilia
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2017's IPOs
Offerings rise, values decline
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Sanofi's Latest M&A Activity
$650m Protein Sciences deal
(p4)

from the editor

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It was less than five years ago that Novartis licensed CAR-T technology from the University of Pennsylvania. At the time, UPenn was already trialing CTL019 in chronic lymphocytic leukemia. The treatment is now on the verge of gaining US approval for children and young adults with acute lymphoblastic leukemia, but the road to success has had its bumps.

Only last summer, Novartis' belief in the technology was called into question when it missed CTL019 off a list of potential blockbusters in its pipeline, and then disbanded its cell and gene therapy business unit with the removal of around 120 job roles and the departure of the unit's head, Oz Azam.

CTL019 made it to the updated blockbuster list by the company's meeting with investors this May, and Novartis now describes its cell therapy platform as "a key pillar of [its] IO strategy". The next milestone will be CTL019's filing in diffuse large B-cell lymphoma, a broader indication for which the company plans to seek approval in both the US and EU in the fourth quarter.

Despite the positive momentum and remarkable potential efficacy of this therapy, its commercial future could still be hobbled by emerging safety or manufacturing issues, or indeed the many challenges involved in rolling it out to enough centers to reach patients. Having acquired Dendreon's Provenge manufacturing facility to produce its CAR-T therapy, Novartis has an ever-present reminder of the danger of hubris when translating scientific breakthroughs into marketable products. It should yet be wary of abandoning its prior caution.

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AstraZeneca Under Soriot: Progress Report
http://bit.ly/2taj0zc
Last week, AstraZeneca's CEO Pascal Soriot was rumored to be preparing for a move to run Teva Pharmaceutical Industries. This week, he's rumored to be staying put. *Scrip* takes a look at the key moments in his tenure at the UK big pharma, and the progress on targets.

Guide To The Turbulent Times At The Top of Teva
http://bit.ly/2uxLu9x
While the rumor mill continues to turn over Pascal Soriot jumping ship from AstraZeneca to Teva, the experience of previous CEOs shows that the chair at the head of the Israeli drug maker's table is a very hot seat indeed.

As Digital Channels Grow In Importance, AZ, Lilly, GSK Seen As Key Engagers
http://bit.ly/2uxLu9x
Digital physician engagement channels appear to be closing in on the traditional face-to-face approach, with China surging ahead on the digital path. The US and China appear more or less in sync when it comes to self-directed web-detailing, while AstraZeneca, Lilly and GSK lead the charts in terms of digital engagement as perceived by healthcare professionals, a new survey shows.

Venture Funding Deals: $688.8m In Financings From Avitide To Zai Lab
http://bit.ly/2u3FTWg
June venture capital financings for emerging companies totaled more than $688.8m, ranging from an undisclosed round for Avitide to a $120m Series B for Rubius Therapeutics.

Tech Transfer Roundup: Janssen, Eisai, Apexian, Innovus And More
http://bit.ly/2vwQgBr
Johnson & Johnson maintains hectic deal-making pace via RA tie-up with Monash and "diabesity" collaboration with UC San Diego.

A $63m VC Round Takes E-Scape Into Clinic With Alzheimer's, Parkinson's Drugs
http://bit.ly/2uDy78y
E-Scape's Series A cash will fund the development of small molecules targeting genetic drivers of neurodegenerative diseases, such as ApoE4 in Alzheimer's disease. The venture capital financing with big pharma backing will be used to take two programs into the clinic.

inside:

Sanofi Defends Corner With $650m Protein Sciences Buy

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Sanofi is expanding its seasonal flu prevention armamentarium to defend its leading position in the influenza vaccine market. It has agreed a deal to acquire privately owned **Protein Sciences Corp.**, of Meriden, Connecticut, for $650m up front and up to $100m in undisclosed sales milestones.

Protein Sciences has developed technology to manufacture vaccines using recombinant proteins produced via the infection of insect cells with engineered baculoviruses. This contrasts with the majority of currently marketed products, which are produced in eggs, a process that takes longer and has the potential to be affected by supply constraints.

FLUBLOK ON THE MARKET

After failing to get significant market traction for its trivalent seasonal influenza vaccine that was approved in the US in January 2013, Protein Sciences won FDA approval for a quadrivalent version in October 2016, for which first sales should be imminent in preparation for the 2017/18 season. Sanofi said that about 300,000 doses of *Flublok* QIV had been prebooked for the 2017/18 season, up from the 150,000 doses of *Flublok* TIV sold in 2015/16 but still a small part of a market in which 140-150 million people are vaccinated in the US each year according to data from Datamonitor Healthcare.

Flublok is the only recombinant protein-based flu vaccine approved by the US FDA, and Protein Sciences' CEO Manon Cox said the company had been "looking for an opportunity to grow its business, particularly in the US." Sanofi said that Flublok was "priced in line with other currently commercialized vaccines."

The acquisition probably comes too late to have an effect on Flublok sales from the 2017/18 US flu season, meaning that the true impact of the product being backed by the market's largest player will not be seen until 2018/19.

UPSTART VS MARKET GIANTS

Despite boasting technology that can deliver vaccines faster and at a lower cost than traditional egg-based vaccines, with additional benefits including improved effectiveness in older people and suitability for people with egg allergy, Protein Sciences has struggled to achieve a decent volume of sales and really break into the flu vaccine market.

The seasonal flu vaccine market is dominated by the big players Sanofi, **GlaxoSmithKline PLC** and **Seqirus** (the business set up by **CSL Ltd.** after it acquired **Novartis AG**'s flu vaccine portfolio in 2015), and the US is by far the largest market for seasonal flu vaccines.

Sanofi reported 2016 flu vaccine sales of €1.52bn; its core brand is *Fluzone*, under which name it markets a high-dose trivalent product particularly targeting the elderly, and a separate (non-high-dose) quadrivalent product.

GSK's *Fluarix* and *FluLaval* brands brought in sales of £414m in 2016.

Seqirus has yet to report its sales figures for calendar 2016/17, which ends June 30, 2017; first-half revenues for the Seqirus business as a whole were $620m. Its core flu brands are *Fluad*, *Flucelvax* and *Afluria*, with Flucelvax offering a cell culture-based alternative to traditional egg-based manufacturing.

AstraZeneca was dealt a setback to its US flu vaccine business when the government recommended against using its *Flumist* nasal vaccine in the current season.

THE ELDERLY CHALLENGE

Seqirus is ahead of Sanofi in developing a quadrivalent vaccine for use in the elderly: its Fluad QIV is expected to take market share from Fluzone HD following its anticipated launch in 2019. Sanofi's Fluzone HD QIV is yet to enter Phase III trials and analysts at Datamonitor Healthcare believe it will not be ready for launch until the 2020/21 season.

"It seems that in the seasonal influenza market, targeting the elderly is profitable, especially when we think about the aging population. It looks like manufacturers are trying to target this market segment with highly potent vaccines, such as the adjuvanted vaccine (Fluad), or the high-dose vaccine (Fluzone High-Dose)," commented Ines Mihel, an analyst with Datamonitor Healthcare."

With the recent data published about the Flublok vaccine testing the vaccine on patients older than 50, it looks like Sanofi will try to promote the Flublok QIV vaccine on the grounds of efficacy as it has demonstrated better protection than the standard vaccines." In a clinical study of 9,000 adults of 50 years of age and older, people who received Flublok QIV were over 40% less likely to get cell-culture confirmed influenza than those receiving a leading egg-produced quadrivalent flu vaccine. Flublok is not approved for people below the age of 18.

Mihel believes that Flublok QIV could "give Sanofi a competitive edge and gain patient share in the elderly population" given that the US market is now primarily driven by quadrivalent vaccines.

However, overall she does not envisage a major shift from egg-based to the more efficient, faster recombinant or cell-based production techniques. "Even if [traditional egg-based production] is not considered a very efficient manufacturing process, I don't think that it will change very soon," she said. Although in theory recombinant vaccines' improved flexibility should allow for a higher strain match to the wild-type virus, Mihel notes that key opinion leaders have commented to Datamonitor Healthcare that manufacturers are in any case constrained by the recommendation of the World Health Organization as to which strain to use, and the US CDC'S Advisory Committee on Immunization Practices (ACIP) follows that recommendation.

Sanofi told *Scrip* that it saw Flublok QIV "as a complement to Sanofi Pasteur's portfolio of flu vaccines" that would "enlarge patients' choices." It will focus initially on the US market. Protein Sciences has existing partnerships for other markets outside the US, which are still being assessed by Sanofi.

PROTEIN SCIENCES' OTHER BUSINESS

Regarding Protein Sciences' other activities, Sanofi said it would assess them after completion of the acquisition. The company offers third-party product development and manufacturing services for vaccines, therapeutics and gene therapies, as well as supplying research antigens and antibodies to the scientific community. It additionally has a pipeline of other vaccine candidates.

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Amicus Renewed Hope For US Oral Fabry Launch

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It's not often that the FDA backtracks on a decision, but in a surprising turn of events, the agency has reversed a decision on **Amicus Therapeutics Inc.**'s oral therapy for Fabry disease, migalastat, agreeing the company can submit an NDA for accelerated review based on existing data.

The company announced on July 11 that it now plans to file a US NDA for migalastat in the fourth quarter, following a series of discussions and written communications with the agency, which could potentially result in a commercial launch in the first half of 2018.

Amicus' stock surged 27% on the news opening the day at $13.02. The news surprised investors because the agency had rejected the company's plan to file for accelerated approval in November and had recommended at the time a new 12-month gastrointestinal study. Amicus had guided that data from the new trial wouldn't be available until 2019, delaying the launch of migalastat in the US by several years.

The sudden turnaround represents a big win for Amicus and could reflect a more business-friendly approach by the FDA under the leadership of Commissioner Scott Gottlieb, who was confirmed in May. President Trump has also pledged to reduce regulations at the FDA to speed drug development, and notably, Trump gave Amicus' founder and CEO John Crowley a nod for starting a biotech focused on rare diseases during his first State of the Union address in February. Crowley's daughter, Megan, who is afflicted with a different rare disease, Pompe disease, attended the State of the Union address and was applauded by Trump.

In a conference call on July 11, however, Crowley downplayed any connection to leadership changes at the FDA or the Administration. "We're in the same review division and largely the same reviewers as well," he said. The change came about after a series of discussions with the FDA and the submission of additional data, he added.

"Since November, we have pursued parallel tracks of both planning for the previously requested GI-based additional Phase III study, while simultaneously engaging in a science and database dialogue with the agency to align on a faster path to a submission without the need for further clinical studies," he said.

Among the information Amicus provided the FDA was new data, mainly cardiac and renal data, as well as a new analysis of existing data, including data submitted to the European authorities, where migalastat was approved in May 2016, Crowley said. The company also provided data from longer-term extension studies and real-world data from the commercial launch of migalastat in Europe, particularly on patients transitioning from existing enzyme replacement therapy. Amicus also provided patient perspectives to the FDA on the unmet need in Fabry and the lack of treatment options in the US.

"All of this has culminated in this confirmation that we are announcing today from the FDA that we may now submit the NDA for migalastat," Crowley said. "We firmly believe that this accelerated US pathway for migalastat is the application of the gold standard in science-based, data-driven and patient-centric therapeutic development."

In a same-day research note, Leerink analyst Joseph Schwartz speculated, "We believe additional data generated on the disease-causing substrate (GL-3) and potentially the regulatory developments ex-US may have contributed to today's announcement and change in the FDA's receptivity." However, he added, "We also cannot rule out the political influence of a new administration (and its inclination toward approving medicines for deadly afflictions) having an influence in today's announcement."

US REPRESENTS LARGEST SINGLE MARKET OPPORTUNITY

Migalastat was approved in Europe last year for patients with Fabry disease with amenable mutations, and it is marketed under the brand name *Galafold*. It is the first oral option for Fabry, but it is targeted to just a subset of patients with the rare genetic disease, those who have amenable mutations based on a proprietary in vitro test. Amicus estimates that 35% to 50% of Fabry patients globally may have genetic mutations amenable to migalastat. In Europe, Crowley said roughly 50 patients are now being treated with Galafold and reimbursed.

Commercial success for drugs targeting ultra-rare diseases like Fabry requires reaching as many patients as possible around the globe.

The US represents the single largest commercial market for the drug, with an estimated 3,000 people diagnosed with Fabry disease, only about 1,500 of whom are treated, according to Amicus. **Sanofi**'s Genzyme unit markets the only other treatment for Fabry in the US, *Fabrazyme* (agalsidase beta), which was first approved in 2003. The commercial market was about $380m in 2016, the firm said.

Current pricing for Fabry disease treatment ranges from $200,000 to $300,000 globally, with the US price being in the higher range of the spectrum, Amicus said. The company's strategy is to price on par with existing therapy.

"We think that reflects the high value of the potential therapy, oral therapy for Fabry disease, which we think Galafold is," Crowley said. "And also, it allows to give some healthcare savings back to the system because you can avoid the infusion associated cost."

The NDA is based on the Phase III Study 011 (FACETS) in enzyme-replacement therapy-treatment naïve patients, in which the drug demonstrated a trend toward efficacy for the primary endpoint, reduction in disease-causing substrate GL-3. The study did show statistically significant benefits on pre-specified secondary endpoints related to reducing diarrhea and improvements in kidney and cardiac function. Progressive accumulation of GL-3 is believed to lead to the morbidity and mortality of Fabry disease, including pain, kidney failure, heart disease and stroke.

A second trial, ATTRACT, measuring migalastat against standard of care enzyme replacement therapy in patients who switched from ERT met the primary endpoint.)

The development road has been a long one for migalastat, extending beyond a decade. The drug, at one point, had a big pharma partner, **GlaxoSmithKline PLC**, but the deal was scrapped when GSK de-emphasized rare diseases.

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CONTINUED FROM COVER

too much," Kappen said. "Our hopes is to see this treatment available sooner."

Other parents also told happier personal stories and advocated in favor of the FDA approval, including Tom Whitehead, whose daughter, Emily, was the first patient treated with CTL019. A healthy Emily appeared with her father at the meeting.

In the pivotal Phase II trial testing CTL019 in pediatric ALL, 82% of patients infused with the drug achieved a complete remission or complete remission with incomplete blood count recovery within three months post infusion. At six months, the overall survival rate was 89%, at 12 months it was 79%.

The morning ODAC panel was dedicated to manufacturing questions, while the afternoon session focused on safety and efficacy. Novartis and its CTL019 manufacturing partner **Oxford BioMedica PLC** largely addressed the panel's concerns about manufacturing quality control, including the design of the CAR construct and viral vector and the potential safety concerns of replication-competent retrovirus (RCR) and insertional mutagenesis, with the understanding that the nature of the treatment means there will always be some variability.

Safety was a bigger concern of the panel members, given that so much about CAR-T therapy and the way patients respond remains uncertain.

Novartis' risk management plan and post-marketing study plans largely appeased the reviewers, however. The company plans to initially target 31 to 35 treatment centers, where it will train and certify physicians. With experience, the company said it will expand the number of centers administering the drug.

A CHANCE TO BE FIRST TO MARKET

The positive recommendation by ODAC gives Novartis an edge in the race to bring the first CAR-T therapy to market and represents the culmination of millions of dollars spent in research. The FDA's approval decision is usually in line with that of its advisory panel. Novartis' BLA for CTL019 has an FDA action date of Oct. 3.

Kite Pharma Inc. is right behind with its own CAR-T therapy, axicabtagene ciloleucel in lymphoma, pending at the FDA.

Novartis Proposes REMS To Address CTL019 Safety

Novartis presented a Risk Evaluation & Mitigation Strategy to FDA's Oncologic Drugs Advisory Committee to address safety concerns associated with the investigational CAR-T therapy tisagenlecleucel (CTL019), particularly cytokine release syndrome. CRS involves a basket of inflammatory symptoms resulting from cytokine elevations associated with T cell engagement and proliferation. It's a sign the treatment is working, and almost all patients experience some reaction, but it can be so severe in some cases the reaction outweighs the benefits. The interleukin-6 inhibitor tocilizumab (**Roche**'s *Actemra*) is often administered to counter the reaction.

Novartis' REMS proposal would be the joint responsibility of the company and administering sites. The plan includes an authorized Novartis representative at each site to train personnel on the adverse events. Only certified prescribers will be allowed to administer CTL019, while the cites will be responsible for assuring staff are trained and have anti-CRS medications stocked. Patients will also be required to stay close to the treatment center for three to four weeks after infusion to monitor for CRS.

The company has also pledged to initiate a post-marketing study to evaluate short- and long-term risks that will run for 15 years.

> Successfully reaching the market with the first CAR-T therapy will be an important victory, but making up lost ground in oncology commercially is what will ultimately appease investors.

The two companies, along with **Juno Therapeutics Inc.**, have been the early pioneers of CAR-T. Juno has followed to the back of the pack after it ended development of its lead CD-19 targeting CAR-T JCAR015 for ALL due to safety, including neurological events and deaths in clinical studies. *(Also see "Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position" Scrip, 1 Mar, 2017.)*

In a show of camaraderie with Novartis, Kite CEO Arie Belldegrun said in a blog post, "I will be Novartis' biggest cheerleader today."

He said: "Today is not about business or competition. Today, we are not rivals. Today is about advancing an exciting technology that has the potential to transform cancer.'

Novartis has invested heavily behind CAR-T, beginning with a high-profile deal signed with the University of Pennsylvania and the lab. of Carl June in 2012 that was believed to have one of the highest upfronts ever for an academic collaboration. *(Also see "A New Industry-Academic Model: Novartis And Penn Make A Splash In Cancer Immunotherapy" Scrip, 26 Nov, 2012.)* While Novartis focused on CAR-T, it fell behind rivals in the other evolving area of cancer immunotherapy, checkpoint inhibitors.

Successfully reaching the market with the first CAR-T therapy will be an important victory, but making up lost ground in oncology on the commercial front is what will ultimately appease investors, especially given the expected expensive and complicated manufacturing process.

Novartis representatives said they will have adequate supply to meet commercial demand. The company also expects that it will be able to speed the process between extracting cells from patients and re-administering them to 22 days from 16 weeks in clinical trials.

CEO Joseph Jimenez has begun to speak more optimistically about the commercial prospects for CTL019; the drug returned to the company's blockbuster hit list this year after being left off last year, and Jimenez recently said one reasons for his enthusiasm is because of the potential for premium pricing given the substantial savings the drug could present to the health care system. *(Also see "Novartis' CAR-T CTL019 Back On The Blockbuster Hit List" Scrip, 1 Jun, 2017.)*

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Top Pharma Firms' Sales At $351bn By 2026

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Despite rising challenges and changing trends in healthcare provision, Big Pharma looks set to expand sales strongly over the next decade as it continues to adapt and identify opportunities for sustained growth.

That's the key takeaway from *Datamonitor Healthcare*'s latest sector analysis - entitled *Big Pharma Outlook 2026* – which predicts that the sector's top 10 pharmaceutical groups will add $25.5bn in sales in the next decade, generating $351bn overall by 2026.

TOP TEN WHO'S WHO

Using Informa's proprietary Pharmavitae Analytics of more than 400 products from the group of top 10 drug makers, Datamonitor Healthcare notes that the top 10 currently have 74 blockbuster drugs representing $172bn in revenue and predicts 36 more blockbusters will join the club between 2016 and 2026. However, 24 blockbusters will lose their status by 2021, with nine more out to 2026.

The ten drug makers assessed are **Pfizer Inc.**, **Sanofi**, **GlaxoSmithKline PLC**, **Roche, AstraZeneca PLC**, **Novartis AG, Merck & Co. Inc.**, **Johnson & Johnson**, **Eli Lilly & Co.**, and **Bristol-Myers Squibb Co.**

By delving deeper into the group's revenue trends, therapy area performances, and strategic drivers, the analysis examines how Big Pharma will need to navigate headwinds to steer towards stronger growth. The correlation between drug pricing and market access will remain a key aspect.

The DMHC report discusses criteria that will determine the best performing companies out to 2026, and identifies those likely to have leading market share gains - and which will lose market share within that period - across the US, the EU's top five economies, in Japan and across in the rest of the world (RoW), and in which specific therapy areas.

ROCHE SEEN TOP DOG BY 2026

The pecking order within the top 10 will change, with US-based Pfizer retaining the top slot up to 2021 but conceding the number one spot to Swiss rival Roche by 2026, the report predicts, and explains why.

Oncology is predicted to maintain the largest proportion of Big Pharma prescription sales out to 2026, with Merck & Co's core immuno-oncology product *Keytruda* (pembrolizumab) becoming the highest selling product, with projected global sales at $9bn. In parallel, PD-1/PD-L1 inhibitors will keep building momentum out to 2026, outperforming other drug classes. Big Pharma's launch portfolio looks set to add $58.3bn in revenues out to 2025, it says.

Trends in deal activity cooled in 2016 but are likely to accelerate this year and beyond, the report says.

It notes that Big Pharma still has numerous headwinds to address out to 2026. The uncertainty surrounding macroeconomic conditions and a challenging payer environment has led to increased scrutiny on drug prices, with reimbursement being increasingly dictated by economic value as well as clinical benefits, making pricing perhaps the biggest issue facing the industry, especially in the US market.

Drug makers also continue to pass through waves of generic entry. The increasing adoption of biosimilars threatens market positions of some but also offers investment opportunity for others.

Strategic trends will continue to lead companies to focus on demonstrating strength within a particular market, it adds.

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CAR-T Companies Hang Onto Novartis' Coat-Tails After Historic FDA Panel Vote

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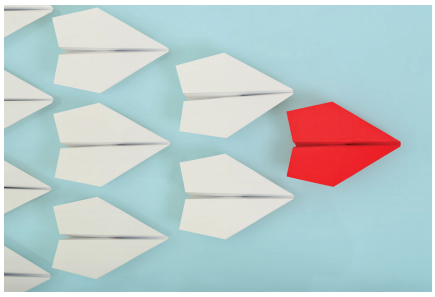
The momentous news that the US FDA's Oncologic Drugs Advisory Committee has recommended approval of **Novartis AG**'s CTL019 has provided a boost not only for the Swiss major but for the rest of the players in the chimeric antigen receptor T cell (CAR-T) market.

The ODAC voted 10-0 in favor of CTL019 (tisagenlecleucel) for pediatric leukemia, a decision that as good as guarantees that the therapy, developed by extracting cells, reengineering them to target CD19 to fight cancer and reinfusing them back into the patient, will be the first CAR-T to get approval (see p1).



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The unanimous vote confirms regulator enthusiasm for the new technology, according to Kevin Harrington, joint head of the division of radiotherapy and imaging at The Institute of Cancer Research, London, who told *Scrip* that while CAR-T had been a topic in academic circles for several years, the FDA thumbs-up is hugely significant – "the word 'landmark' is the only one I can think of."

His views were echoed by Datamonitor Healthcare analyst Hardik Patel who told *Scrip*: "I think the fact that this was a unanimous vote for the use of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) is a very good sign for CAR-Ts in general." He noted that much of the conversation at the ODAC "seemed to revolve around whether the

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known side effects of the drug were severe enough to outweigh its benefits, but all of the panelists seemed to agree that the potential benefits of treatment were worth the risks."

BIGGER CHALLENGES IN LARGER PATIENT POPULATIONS

However, the high level of unmet need in ALL likely aided in the positive assessment, Patel said, "and the risk/benefit analysis may be a bit more difficult to evaluate for other therapies seeking approval for indications with more viable approved treatment options."

ICR's Harrington agrees, alluding to safety issues that rival CAR-T developer **Juno Therapeutics Inc.** has encountered; it ended development of its lead CD-19 targeting CAR-T – JCAR015 – for ALL due to neurological events and deaths in clinical studies in March. *(Also see "Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position" Scrip, 1 Mar, 2017.)* As for **Kite Pharma Inc.**, it has submitted KTE-C19 (axicabtagene ciloleucel) through a rolling submission in the USA but for a far larger patient population than ALL, namely aggressive non-Hodgkin's lymphoma.

INITIAL INVESTOR RESPONSE LUKEWARM

Despite the enthusiasm that greeted the FDA vote, investors are a little more cautious. At 2.45pm UK time, Kite shares had dipped 1% to $103.72, while Juno was basically flat at $28.04. France's **Cellectis SA**, which recently announced that the first patient has been dosed in a Phase I study testing its allogeneic, or 'off-the-shelf' therapy CAR-T known as UCART123, has also barely moved to €22.05. As for Novartis, its stock was actually down 0.6% to 80 francs *(Also see "Cellectis Moves First Off-The-Shelf CAR-T Into US Clinical Trials" Scrip, 3 Jul, 2017.)*

There are still a host of challenges for all the companies in the CAR-T field, notably manufacturing drugs that have to be tailored to each individual patients and training doctors at specialist centers to administer the therapies, not to mention the issue of price. However, for the moment, companies, clinicians and patients are celebrating.

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US Biopharma Offerings Rise, Values Decline At Mid-Year

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Average IPO return has gone down, but that hasn't slowed the momentum of new offerings

As more biopharmaceutical companies have joined the US stock market via initial public offerings in the first half of 2017, the average IPO return has gone down, but that doesn't seem to have slowed the momentum of new offerings, which at 19 put this year on track to beat 2016's total of 30 IPOs.

Market observers said at the start of this year that they expected to see fewer drug developers launch IPOs in 2017 than during the past few years, but that doesn't seem to be the case. After a relatively slow first quarter when just five companies priced IPOs, there were 14 offerings in the second quarter. *(Also see "After Tocagen Thaws IPO Freeze, Verona And Zymeworks Bring April Total To Three" Scrip, 28 Apr, 2017.)* However, with an average return of 14% as of June 30, the IPO class of 2017's performance is slipping compared with averages noted earlier in the year. That could hurt future biopharma offerings, if investors looking for growth stocks decide to look away from this sector.

Scrip has looked periodically at the performance of companies that have gone public this year and the average return was 22.8% for the 13 companies that launched IPOs as of May 19. *(Also see "Finance Watch: Two More US Biopharma IPOs And Two New European VC Funds" Scrip, 20 May, 2017.)* Before that, the average return was 20.6% as of May 10. *(Also see "Biopharma IPOs Gain Momentum As Three More Launch In The US" Scrip, 10 May, 2017.)*

The company with the highest return so far this year is the New York-based immuno-oncology company **BeyondSpring Inc.** whose stock was up 114.4% at the mid-year point. BeyondSpring, which went public in March, was the only biopharma company in 2017 to price an IPO at $20 per share and the only one to produce a triple-digit return versus the offering value as of June 30. *(Also see "Finance Watch: Two New VC Funds Raise $500m; One New US IPO; And Galena's 'Strategic Review'" Scrip, 17 Mar, 2017.)*

At the other end of the value spectrum, **ObsEva SA** provided the biggest loss of any therapeutics company to launch an IPO in the US this year with a 43% loss as of June 30. The Swiss firm specializing in therapeutics for women's reproductive health was one of three first-time offerings by drug developers in January. *(Also see "IPO Update: Three Biopharma Offerings In January Contrast With Last Year's Slow Start" Scrip, 6 Feb, 2017.)*

Eleven of the 19 biopharma companies to go public in the US were trading in positive territory – at least 16.3% above their IPO prices – as of June 30 (*see table below*). A scan of July 13 stock prices shows that almost two weeks later, one more company

2017 US Biopharma IPOs And Performance At Mid-Year

COMPANY	IPO PRICE	JUNE 30 CLOSING PRICE	RETURN
AnaptysBio Inc. (ANAB)	$15	$23.93	59.5%
Jounce Therapeutics Inc. (JNCE)	$16	$14.03	-12.3%
ObsEva SA (OBSV)	$15	$8.55	-43%
BeyondSpring Inc. (BYSI)	$20	$42.88	114.4%
Therapix Biosciences Ltd. (TRPX)	$6	$6.99	16.5%
Tocagen Inc. (TOCA)	$10	$12.03	20.3%
Verona Pharma PLC (VRNA)	$13.50	$11.65	-13.7%
Zymeworks Inc. (ZYME)	$13	$8.35	-35.8%
Ovid Therapeutics Inc. (OVID)	$15	$10.49	-30.1%
UroGen Pharma Ltd. (URGN)	$13	$18.06	38.9%
Biohaven Pharmaceuticals Holding Co. Ltd. (BHVN)	$17	$25	47.1%
G1 Therapeutics Inc. (GTHX)	$15	$17.44	16.3%
argenx SE (ARGX)	$17	$21.21	24.8%
Athenex Inc. (ATNX)	$11	$16	45.5%
Immuron Ltd. (IMRN)	$10	$8.60	-14%
Dova Pharmaceuticals Inc. (DOVA)	$17	$22.29	31.1%
Mersana Therapeutics Inc. (MRSN)	$15	$13.97	-6.9%
Aileron Therapeutics Inc. (ALRN)	$15	$11.15	-25.7%
Avenue Therapeutics Inc. (ATXI)	$6	$7.95	32.5%
Average Return			**14%**

has slipped below its offering price; the brain cancer therapy developer **Tocagen Inc.** closed at $9.94, or just 6 cents below its IPO value. *(Also see "After Tocagen Thaws IPO Freeze, Verona And Zymeworks Bring April Total To Three" Scrip, 28 Apr, 2017.)*

Only time will tell how drug developer stocks will hold up this year based on company-specific news, such as clinical trials results, or broader concerns, such as more favorable treatment of biopharma by the US FDA under new commission Scott Gottlieb or – conversely – government action on drug pricing. But if stock valuations continue their declining trend, investors may decide to look elsewhere for growth.

The IPO-tracking firm Renaissance Capital noted that 50% of the 52 US IPOs in the second quarter, which raised $11bn, were completed by technology and health care companies – and all the health care offerings were done by biopharma companies. Those tech and biotech investments were driven by investors seeking growth companies, Renaissance said, with an expectation that that will continue in the third quarter.

However, it's important to note that when it comes to drug developer offerings, those IPOs also are helped by significant participation from insiders – investors who supported the therapeutics firms while they were privately held.

Speaking of private investors, Renaissance noted that venture capital-backed companies did particularly well during the second quarter when they went public. The average return for venture-backed IPOs was 23% versus 13% for all second quarter offerings and that higher return was driven by tech companies and biopharma firms "with only a few biotechs ending the quarter below issue," the firm said in its second quarter US IPO market report. That's good news for drug developers that are raising venture capital right now, because VC firms are more likely to raise money and they're more likely to invest that capital if the IPO market is performing well – and that seems to be playing out.

The National Venture Capital Association and the VC-tracking firm Pitchbook reported in their recent Venture Monitor update that 274 pharma and biotech companies raised $4.58bn during the first two quarters of 2017, which is more than half of the full-year totals for 2016 when 534 US companies brought in $8.09bn in venture capital.

Similarly, 556 life science companies, including drug developers as well as medical device and diagnostic firms, raised $7.44bn during the first half of this year versus last year when 1,026 raised $11.9bn.

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What Does Ocular's Latest CRL Mean for Dextenza?

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Like two ships passing in the night, **Ocular Therapeutix Inc.**'s request to extend the review period for its US new drug application (NDA) for a post-surgical ocular pain product was followed roughly 24 hours later by a complete response letter to the NDA for *Dextenza* (dexamethasone insert).

Ocular's July 10 filing to the US FDA intended to close out the responses to the agency's Form 483 letter issued in May regarding manufacturing concerns for Dextenza, but while the agency acknowledged receipt of the information it already had decided to issue a CRL, pushing back an approval decision indefinitely. Without knowing that the FDA had its own response to the NDA in mind, Ocular acknowledged that the submission of new manufacturing specifics was a major amendment to the pending application, which is why the company requested a three-month extension of the July 19 action date.

Bedford, Mass.-based Ocular had hoped that corrective measures it made following a May pre-approval site inspection of its manufacturing site – including replacing an aluminum blade with a stainless steel blade – would be sufficient to address the concerns in the Form 483. The biotech also is working to produce a commercial batch of Dextenza for the FDA's review using the revised equipment, and indicated on a July 10 investor call that it believed it could produce the material in time for FDA to approve Dextenda by Oct. 19, if it granted the three-month extension of the user fee date.

Market analysts covering Ocular offered strongly divergent takes on the news, with JMP Securities suggesting in a July 12 note that the FDA might soon determine that the company's July 10 filing was adequate to address its concerns, possibly putting Dextenza on track for approval by Oct. 19. By contrast, BTIG Equity Research posited that Ocular might need to refile the NDA entirely, pushing the product's approval timeline back by as much as 12 months.

CRL DOES NOT REQUEST NEW TRIAL

Ocular revealed in February that its NDA – subject to a previous CRL in 2016 also tied to manufacturing issues – had been accepted by the FDA with a July 19 action date. After receiving the second CRL on July 11, the company pointed out that the FDA had not cited any efficacy or safety questions about clinical trial data for Dextenza – which has been tested in more than 550 clinical trial subjects for post-surgical ocular pain – nor indicated that any new clinical trials would be required for approval.

"We believe the submission of our latest response to the Form 483 and concurrent submission of the amendment to our NDA can support an acceptable regulatory pathway for the approval of Dextenza," said Ocular Founder and CEO Amarpreet Sawhney during a July 10 call prior to issuance of the CRL. "We continue to be in close communication with the FDA to determine the best course of action in an effort to successfully bring Dextenza to market as quickly as possible. There is no guarantee that the FDA will consider our amendment as a major amendment, although we feel we have adequately addressed the matters related to the 483."

How the FDA responds to the company's July 10 filing is a subject of broad disagreement among analysts. "OCUL has filed three responses to close-out the previous Form 483 and the FDA has acknowledged receipt of the responses, but has not had a chance to review them," JMP's Donald Ellis wrote in a note maintaining a "market outperform" rating for Ocular Therapeutix. "Importantly, the CRL was filed prior to OCUL's response and not as a result of its response."

"We believe that if the FDA had waited a few more days to issue the CRL, it would have assessed that OCUL had rectified the issues raised in the Form 483 and did not require a CRL," he continued. "We believe OCUL will most likely receive a Class 1 review and a new PDUFA date in approximately 90 days."

If FDA decides upon a Class 1 review (which would set a 60-day review window), that could mean an approval decision before Oct. 19, the analyst pointed out. One of FDA's concerns pertained to aluminum particulate found in some batches of Dextenza, which Ocular believes it has solved by replacing an aluminum cutting blade with one made of stainless steel.

"Dextenza inserts are formed by cutting longer strands [of the therapeutic substance] to final size," Sawhney explained on the investor call. "All inserts are then inspected under magnification to ensure that they meet the specifications for being essentially free of particulate matter before being packaged and released for clinical or commercial use. The piece of equipment employed for cutting the strands had functioned within limits until early this year, when it began showing signs of higher particulate generation due to wear from the aluminum cutting arm and other parts."

"As a result of our investigation, we determined that the piece of manufacturing equipment used for cutting strands is the most probable source of particulate," he added. "We have replaced the aluminum cutting arm with a stainless steel arm and made certain other changes that substantially address the source of particulate generation."

BTIG analyst Dane Leone, however, expressed doubts that these changes would be sufficient to address the FDA's concerns. His July 12 note maintained a "neutral" rating for Ocular shares, pointing to "the breadth of issues stated within the recent manufacturing inspection."

"We would assume a roughly 12-month delay for Dextenza approval," Leone added. "We think that management will pursue the closeout of the Form 483 letter and then resubmit the NDA – which restarts the clock for FDA review."

Even despite a second CRL, Biomedtracker rates Dextenza as having an 87% of approval, which is 8% higher than average for ophthalmology drugs that have reached the end of Phase III.

Dextenza is a sustained and tapered release of dexamethasone depot administered via a hydrogel punctum plug. It uses Ocular's proprietary hydrogel technology, which employs polyethylene glycol (PEG) to deliver sustained and therapeutic levels of the drug to targeted ocular tissues.

The company says the product's microparticles can be tailored to provide the desired duration of therapy ranging from days to months, and are compatible with a wide range of ophthalmic medications. The hydrogel formulation provides containment, localization and protection from inflammatory response, enabling sustained delivery of drugs to the eye. The drug is inserted non-invasively through the punctum.

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Almirall Knocked Back By US Woes, Could Affect Other Companies Too

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The US is often seen, quite rightly, as a market opportunity for Europe's pharmaceutical companies, but it can also be an unpredictable market where setbacks can rapidly follow each other in what might seem as an unremitting sequence. Barcelona, Spain-headquartered **Almirall SA** has just been afflicted by three such setbacks, leading to a lowering in its sales and earnings guidance for 2017.

Almirall's US business, Aqua, has been adversely impacted by what seems to be the inappropriate use of its patient assistance programs by certain US pharmacies, the continuation of inventory destocking already seen in the 2017 first quarter, and the launch of a generic version of immediate-release tablets of *Acticlate* (doxycycline hyclate) 75 mg and 150 mg, company executives explained to analysts in a telephone briefing on July 10.

The news of the US setbacks and an accompanying profit warning by the company led to an 18% decline in Almirall's share price to €9.5 per share on the Madrid Stock Exchange in the morning of July 10, before the stock recovered to €10.2 by midday. Analysts at Jefferies noted that the US dermatology market is challenging, with payers increasingly paying close attention to the market and putting pressure on rebates and discounts.

Almirall said that its EBITDA would decline to €140-170m during the year compared with previous guidance of mid-single digit growth on 2016, and total revenues would decline by low double-digits, compared with previous guidance of low- to mid-single digit growth. In 2016, the company's EBITDA was €227.6m and its revenues were €859.3m.

LEGAL ACTION AGAINST PHARMACIES

Perhaps the most serious of the adverse issues in the US, and one that might affect other companies in the country, is the concern over inappropriate use of its patient assistance programs via pharmacies. "It appears that ways were found to cheat the system," Almirall executives told the briefing. Although they declined to go into specifics, the inappropriate use, across its product portfolio, has been serious enough to lead to legal action against certain pharmacies, they noted. New checks and controls have been introduced into the system to prevent recurrence of the issue. The program gives co-payment assistance to patients through the use of a savings card. The issue is being monitored on a daily basis.

The Spanish company has also continued to suffer from inventory destocking that has continued during the second quarter and is expected to have an adverse impact of €25-30m on financial results in the first half of 2017. Management of the supply chain has been strengthened, and stockpiles are now down to a matter of weeks rather than months, and we are now confident we have this issue under control, the executives said.

Finally, the launch of a generic version of Acticlate immediate-release at an initial discount of 10% to Almirall's Acticlate's list price is expected to adversely affect sales of the branded product. The company is responding by allowing the launch of an authorised generic by **Teva Pharmaceutical Industries Ltd.** Nonetheless, previously expected sales of Acticlate in the US will be affected by all three issues, destocking, the patient assistance program and the authorised generic.

Aqua was acquired by Almirall in Dec. 2013 to drive the Spanish company's expansion into the US dermatology field, and demand for its products was said to still remain strong *(Also see "Almirall Eyes Top Specialty Dermatology Role After its AstraZeneca Deal" Pink Sheet, 11 Nov, 2014.)*. Almirall CEO Eduardo Sanchiz pointed out that Almirall's ex-US business, in Europe and elsewhere, was performing in line with expectations. "We have a good track record of balancing strategic/business development with financial performance," Sanchiz noted.

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Roche Supply Decision Under Investigation

It all started in 2010, when the Co-Re-Na pharmaceutical depot in Turkey refused to sign a contract offered by **Roche**, which asked it not to sell the company's products outside the country. After the contract refusal, the Swiss firm decided to halt all sales of its products to the depot, with industry insiders alleging that the company also convinced some other depots and companies not to provide drugs to Co-Re-Na.

Almost immediately, Co-Re-Na applied to Turkey's Competition Authority claiming that Roche had breached Turkish Competition Law. However, the board rejected the application, claiming there was no legal ground for an investigation. Things started to change again when Co-Re-Na applied to Turkey's Council of State to appeal the Competition Authority's decision, and in December 2016, the Council annulled the Authority's earlier decision, stating that Roche's refusal to supply drugs to the depot breached relevant laws and regulations. The Competition Authority decided to start an investigation into Roche at the beginning of July.

It is not the first time for Roche to be investigated in Turkey. Several former Roche executives in the country were jailed last year in a corruption probe over the local pricing of an epoetin beta product.

The new investigation goes to the heart of the parallel trade problem in Turkey, and companies' efforts against it, that may set an important precedent. As drugs are much cheaper in Turkey than most European countries, many products are finding their way to nearby European countries like Bulgaria, Greece, Romania, Croatia and even Italy.

From the editors of *PharmAsia News*.

Ahmet Sevindik
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Provenge To Drive Sanpower Growth And Wider China Cell Therapy Market?

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After completing the acquisition of **Dendreon Corp.**, Sanpower hopes the first ever cross-border deal by a Chinese company to buy an innovative product will not only boost its own prospects but could also promote the wider development of China's immunotherapy standards and regulations.

At the heart of the deal is *Provenge* (sipuleucel-T), the first and only US FDA-approved cellular immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). The product could help set a benchmark to perfect and optimize the drug review system for other cellular immunotherapies in China, Sanpower's spokesperson Guikan Hua said.

Through this transaction, Sanpower acquired not only Provenge but also Dendreon's world-class cellular R&D platform, production facilities, logistics and distribution, and also its quality control standards and quality assurance system, which address precisely the challenges and risks that China's immunotherapy developers have been struggling to solve.

Furthermore, "The acquisition will effectively promote establishment and improvement of China's cellular immunotherapy in terms of quality control and the regulatory system, which will also provide a reference for other immunotherapy drugs such as CAR-T and TCR-T," predicted Shuren Zhang, the vice president of the China Anti-Cancer Association (CACA).

SANPOWER'S SYNERGY, M&A STRATEGY

The acquisition of Provenge is an important step in the area of precision medical treatment for Sanpower, which will allow the group to expand its umbilical cord blood banking resources in China and elsewhere in Asia from the basics to practical application, together with the company's senior care services and genetic testing.

Currently Sanpower has six million elderly users of its AnKangTong healthcare services arm, providing a large potential patient base for Provenge in the future. And the genetic big data from its umbilical cord blood banking with a storage capability of one million units will also provide the basis for developing precision medicine.

In a recent interview with *Scrip*, Dendreon's CEO James Caggiano noted that through the first step of acquiring Dendreon, Sanpower sees immunotherapy and stem cell therapies as the wave of the future and plans to build a portfolio of those products, which it expects to bring to China and Southeast Asia. *(Also see "Under Sanpower, Can Provenge Finally Have A Happy Ending?" Scrip, 3 Jul, 2017.)*

In the future, Sanpower will leverage its expertise in senior care, hospitals, umbilical cord blood banking, and stem cell storage, together with further development in precision medicine, "to create a new healthcare platform covering whole industry chain," Sanpower's chair Yafei Yuan commented.

The firm also has an internal investment team of 50 to 60 members to screen overseas acquisition opportunities, and is seeking targets that can synergize with Sanpower's existing healthcare businesses.

In 2014, Sanpower acquired Israel's largest home healthcare provider Natali Seculife Holding Ltd. for $70m. And later in 2016, its China A-share listed subsidiary, Nanjing Cenbest, set foot into the biopharmaceutical business by acquiring a 20% equity stake in Singapore's Cordlife Group Limited and 76% of Sinocord, as well as setting up a buy-out fund to acquire NYSE-listed China Cord Blood Corporation for CNY5.7bn ($840m).

In January this year, Sanpower signed a strategic collaboration agreement with China CITIC Bank to establish a global healthcare M&A fund of $2.9bn in a bid to boost Sanpower's healthcare and biotechnology investment strategies. The fund will focus on investing and acquiring overseas projects, importing advanced technologies, and improving industry supply chains.

As for the Dendreon deal, Caggiano said that there will be no disruption or changes to the company's technology, manufacturing, operations, or distribution process and that product for the US will continue to be made in the USA.

But for Chinese patients, Yang Wang, senior vice president for cross-border investment at Sanpower, expressed the possibility of building a local manufacturing facility to save costs, aiming to provide products at a cheaper price.

Wang noted that the company will learn from the practical experience of marketing Provenge in the US, and discuss with authorities to create an innovative insurance system to provide better access to the new immunotherapy for patients with fewer financial power.

REGULATORY CLIMATE IMPROVING?

The Dendreon deal may also have other implications in the policy field in China, where currently there is no approved cellular immunotherapy. The registration review pathway for such products and the related regulatory system including Good Manufacture Practice, Good Clinical Practice and Good Supply Practice are still under development, which could possibly challenge and impact the technology transfer and launch of Provenge in China. Chinese industry experts have showed their concerns.

"China is not far behind the US and Europe in the field of basic research in cellular immunotherapy, but there is still a gap between China and the developed countries regarding the industrialization of research results, clinical application and regulations," CACA's Zhang noted.

After the death last year of Zexi Wei, who received experimental immunotherapy treatments for synovial sarcoma after reading about these in a promoted result on the Chinese search engine Baidu, China has tightened supervision of immunotherapies. Currently the China FDA is in the process of drafting technical guidance for clinical evaluation and clinical studies for cellular immunotherapy, and the industry expects the authority to improve the regulations to accelerate approvals, Zhang said. Sanpower Group's president Huaizhen Yang said in an

interview with local media that Sanpower has already started to prepare the technology transfer and for the filing of a new drug registration application with the China FDA, while the company is proactively communicating with relevant authorities. Yang noted that Sanpower had received positive feedback from the authorities.

Regulatory reforms in China since last year have been sending positive signals to cellular therapy developers. In December 2016, the CFDA published a technical guideline for research and evaluation of cell-based products, which for the first time clarified cellular immunotherapy as a pharmaceutical product instead of a therapeutic technology.

In May this year, the CFDA issued three promoting policies to accelerate approvals for drugs that address unmet medical needs, and to support clinical use of innovative drugs by accepting overseas clinical trial data and global multicenter studies.

Most recently in June, the CFDA became a member of the International Council for Harmonization (ICH), which would benefit international companies and innovation-driven firms to speed up the entries of their new drugs in China.

PROSTATE CANCER MARKET IN CHINA

The incidence of prostate cancer in China and Asia was lower than in Europe and the US in the past, but in the last 10 years, it has risen rapidly in China with an annual growth rate of 12%, ranking the sixth most common cancer in Chinese males, according to data from Urological and Male Reproductive System Tumors Committee under the CACA.

As the end of 2015, there were more than 220 million people aged over 60 in China, and more than 18% of the population will be over the age of 60 in 2020. Given the huge population base of the aged, it is expected that prostate cancer will continue to grow accordingly.

Currently, androgen deprivation therapy is the main treatment of advanced prostate cancer in China. Major products include leuprorelin from **Takeda Pharmaceutical Co. Ltd.**, Beijing Biote Pharmaceutical and **Livzon Pharmaceutical Group Inc.**, goserelin from **AstraZeneca PLC**, and triptorelin from **Ipsen** and **Ferring Pharmaceuticals Inc.**

The latest approved treatment for metastatic castration-resistant disease was **Janssen Pharmaceuticals Inc.**'s *Zytiga* (abiraterone acetate), which was cleared for use in combination with prednisone in May 2015 and was launched in January 2016. Zytiga has been included into the reimbursement drug list in some cities.

Other drugs for mCRPC undergoing clinical trials in China include *Jevtana* (cabazitaxel) from **Sanofi**, *Xtandi* (enzalutamide) of **Astellas Pharma Inc.**, and *Xofigo* (radium Ra 223 dichloride) from **Bayer AG**.

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J&J's First-In-Class Tremfya Poised To Join A Crowded Psoriasis Market

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Johnson & Johnson will launch its first-in-class interleukin-23 inhibitor *Tremfya* (guselkumab) at a premium price in the US that is nonetheless competitive with other new biologic entrants for moderate-to-severe plaque psoriasis. The company announced the FDA approval of Tremfya on July 13, with plans to launch the drug within two weeks.

Tremfya will join a crowded market for psoriasis drugs, one that has grown even more so in the last two years, with the launch of a new class of biologics that block IL-17, including **Novartis AG**'s *Cosentyx* (secukinumab) in 2015, **Eli Lilly & Co.**'s *Taltz* (ixekizumab) in 2016 and **Valeant Pharmaceuticals International Inc.**'s *Siliq* (brodalumab) in 2017. *(Also see "Formulary Focus: Cosentyx Navigating Tightly Managed Psoriasis Market" Scrip, 1 Jun, 2015.)*

J&J set the US wholesale cost for Tremfya at $9,684 for a 100 mg pre-filled syringe, a single dose, or roughly $58,100 annually. The price is line with the cost of the first-in-class IL-17 blocker Cosentyx, which launched at a list price of around $58,000. Despite the crowded market for psoriasis therapies, including well known anti-TNFs like **AbbVie Inc.**'s *Humira* (adalimumab) and J&J's own IL-12/IL-23 inhibitor *Stelara* (ustekinumab), Tremfya is expected to be an important near-term growth driver for J&J. The successful launch of Cosentyx highlights the market opportunity for effective new psoriasis drugs. Cosentyx generated $1.1bn in 2016, becoming a blockbuster in its first full year on the market.

Top brass at the diversified pharma highlighted the Tremfya launch as one of two new drugs that would drive growth within J&J's immunology franchise during a pharma-focused investor briefing earlier this year; the other is sirukumab for rheumatoid arthritis. *(Also see "J&J Forges Ahead In Immunology Despite Competitive Dynamics" Scrip, 18 May, 2017.)*

As a first-in-class agent, Tremfya offers a new alternative to patients. IL-23 works upstream in the inflammatory cascade compared to IL-17 or TNF, which the company believes could offer efficacy advantages.

The BLA submission included a Phase III trial comparing guselkumab head-to-head against Humira, and demonstrated superiority on skin clearance. The drug also demonstrated effectiveness in patients who had an inadequate response to treatment with Stelara. J&J is now running a head-to-head trial versus Cosentyx. The full data package included three Phase III trials that enrolled more than 2,000 patients.

Tremfya does offer a dosing advantage over existing therapies as well. It is administered as a single 100mg injection every eight weeks, following starter doses at weeks 0 and four. Labeling for Cosentyx calls for a 300 mg injection every four weeks, following weekly starter doses for the first four weeks, though it says a 150 mg dose may be acceptable for some patients. The dosing recommendation for Humira for psoriasis is every other week.

J&J announced the regulatory filing in November and cashed in a priority review voucher to expedite the review.

J&J also is looking to expand the indications for Tremfya, with a Phase III trial in psoriatic arthritis expected to begin in the third quarter.

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Roivant's Ramaswamy Woos Celgene's Fouse To Lead Dermavant

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Roivant Sciences GMBH has tapped a high-profile pharma executive to lead its dermatology start up **Dermavant Sciences Ltd.** as executive chair – Jacqualyn "Jackie" Fouse, the former president of **Celgene Corp.** Her plan is to turn Dermavant from an early-stage drug development company into a medical dermatology leader, with an initial emphasis on novel topical formulations.

"There is a great need in medical dermatology for innovation," Fouse said in an interview on July 10, the day the appointment was announced. "I think we are on the brink of being able to [deliver] on that because we understand more about these diseases than we have in the past and there are a number of classes of compounds that have been brought to market, either biologics or orals, that have worked well in some of these diseases but [we] really still need to come with novel formulations for them."

Fouse's top priority at Dermavant will be moving the existing pipeline forward – including a Phase II drug for atopic dermatitis – and signing more deals to bring in additional assets. Her experience at Celgene should be an asset on the partnering front.

"The model is going to be a partnering model. We aren't going to do basic research," she said. "The experience at Celgene working with my colleagues on the partnering strategy that we developed and executed on over the years has given me a lot of experience working with these small companies and how to align interests."

Celgene only announced Fouse's departure in February, with her "retirement" from the company effective on June 30. The news came about a year after the company appointed Mark Alles CEO, while giving Fouse the title of president and chief operating officer. Many industry watchers have been wondering where the experienced biotech leader would land next. Roivant founder and CEO Vivek Ramaswamy said the first thing he did when he heard the news about Fouse leaving Celgene was to get in touch with her.

"Her reputation is among the strongest of any of the executives I've met in the pharmaceutical industry and the diversity of experience she has and her versatile style really fits with our model," Ramaswamy said.

What made her the right person for the job, however, is that she understood and agreed on the mission behind Dermavant, he said.

"Dermatology has fallen through the cracks and it's not for lack of affecting millions of people," he said. "Our goal in establishing Dermavant was to focus on novel, non-steroidal mechanisms of action. What we needed was a leader who saw that same gap that we did and had the qualities of leadership to be the agent to solve that problem."

ROIVANT'S PAST RECRUITMENT FORM

Riovant has successfully recruited other high-profile biotech executives to helm its subsidiary companies, including most recently David Hung, the former **Medivation Inc.** CEO, who successfully negotiated a sale of the company to **Pfizer Inc.** last year. Hung joined Riovant's neurology-focused subsidiary **Axovant Sciences Ltd.** in April, taking the helm of a company with a late-stage Alzheimer's candidate that is getting a lot of attention from investors. *(Also see "Full Circle: David Hung Looks Forward To Axovant's Alzheimer's Data, Reflects On Medivation" Scrip, 27 Jun, 2017.)*

Roivant has established five subsidiary companies since Ramaswamy, a young biotech investor, started the company in 2014, with a focus on establishing a new kind of pharmaceutical company, one with a centralized operation to focus on R&D and corporate functions, and therapeutically-focused subsidiaries, built through in-licensing underappreciated assets. In addition to Dermavant and Axovant, Roivant has also launched the women's health-focused company **Myovant Sciences Ltd.**, the rare disease specialist **Enzyvant Sciences GMBH** and most recently **Urovant Sciences**, specializing in urology.

Dermavant, meanwhile, is focused on three drugs in the pipeline, including lead asset RVT-501, a topical phosphodiesterase-4 inhibitor in Phase II clinical testing for mild-to-moderate atopic dermatitis. Two other drugs in earlier development are RVT-502, also known as cerdulatinib, a dual spleen tyrosine kinase (Syk) and janus kinase (JAK) inhibitor in development as a topical formulation for various skin conditions, and RVT-201, a caspase-1 inhibitor.

Roivant in-licensed worldwide rights to RVT-501 from **Eisai Co. Ltd.** in November 2015; the terms of the deal were not disclosed.

While there have been limited treatment options for patients with atopic dermatitis aside from steroids, two new drugs have launched for the painful skin condition in the last year, Pfizer's topical *Eucrisa* (crisaborole), a topical PDE-4 inhibitor, and the first biologic, **Regeneron Pharmaceuticals Inc./Sanofi**'s *Dupixent* (dupilumab), which is off to a strong launch .

RVT-501 would apparently compete against Eucrisa if it reaches the market, but Fouse said there may be opportunities to differentiate RVT-501. The company is testing two different concentrations of the drug, a 0.2% formula previously tested by Eisai, and a 0.5% formula that could deliver enhanced efficacy, she said.

Despite the competitive dynamics in dermatology, Fouse said she envisions a niche for Dermavant between the big pharma companies that have more of an opportunistic approach to the field and the small dermatology specialists that have less of a science-driven approach when it comes to developing new drugs.

But the company's focus will remain largely on novel topical formulations, not necessarily biologics or systemic medicines, at least in the near-term. "Right now, we see the biggest area of need is brining novel classes of compounds into topical formulation," she said. "That is going to require a lot of work on the formulation side."

Biotech investors waiting for the next big IPO to come from Roivant will have to wait, however. The company is fully funded and will remain private for now, both Fouse and Ramaswamy confirmed.

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Phase III Updates Bode Well For Roche's Emicizumab

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Results from the Phase III HAVEN 1 study published in the *New England Journal of Medicine* and a positive reception of data presented at the International Society on Thrombosis and Haemostasis (ISTH) Congress in Berlin bode well for approval of **Roche**'s emicizumab in hemophilia.

Emicizumab (ACE910) is a bispecific monoclonal antibody that binds to both Factor IXa and X. The drug is being positioned as a convenient, once-weekly subcutaneous therapy and alternative to frequent intravenous injections and infusions for patients who developed inhibitors to Factor VIII. After developing inhibitors, treatment options are more limited and very expensive. Options for patients who develop inhibitors include **Shire PLC**'s prothrombin coagulant complex *FEIBA* and **Novo Nordisk AS**'s *NovoSeven*.

Emicizumab's subcutaneous once-weekly administration represents an advantage that is "far preferable to current bypassing agents," Jefferies analyst Jeffrey Holford said in a July 10 note.

"This is a huge advantage, because the need for frequent intravenous infusions has a negative impact on the quality of life (QoL) of hemophilia A patients," the analyst wrote.

Roche has submitted data from two Phase III studies – HAVEN 1 and HAVEN 2 – to support regulatory filings for emicizumab with the US FDA and the European Medicines Agency. The company has two other Phase III studies ongoing – HAVEN 3 in patients with no Factor VIII inhibitors and HAVEN 4 in patients with or without inhibitors.

Data from HAVEN 1 were presented at the ISTH meeting and published in the *New England Journal of Medicine* on July 10.

The study tested the drug in 109 patients aged 12 and up who had hemophilia A, including patients who developed inhibitors to Factor VIII, and who were previously treated with bypassing agents given on demand or for prophylaxis. In the study, patients who had prophylaxis with emicizumab had a significantly lower rate of bleeding compared with bypassing agents used on demand in case of events. The hazard ratio for this result was strong, with an 87% reduction in risk of bleeding ($p<0.0001$).

Roche also reported that, after 31 weeks, patients in the emicizumab prophylaxis arm were much more likely to have zero bleeds than those in the comparator arm (62.9% versus 5.6%), as well as lower rates of spontaneous bleeds, zero treated joint bleeds and zero bleeds overall.

"A clinically meaningful and statistically significant improvement in health-related quality of life (HRQoL) measured at 25 weeks, using two validated instruments (Haem-A-QoL and EQ-5D-5L), was also observed," the company said in a statement.

Emicizumab has generated enthusiasm, but there have been concerns about safety following the report of a death in the HAVEN 1 study, though investigators said that it was unclear whether the event was related to the test drug. In that case, a patient had a serious rectal hemorrhage, was treated with bypassing agents and developed thrombotic microangiopathy (TMA).

"After the data cutoff for the primary analysis, thrombotic microangiopathy developed in one additional participant five days after his previous emicizumab dose and after four consecutive days of treatment with activated prothrombin complex concentrate for rectal hemorrhage; the rectal bleeding was recurrent and eventually fatal. As assessed by the investigator, thrombotic microangiopathy was resolving at the time of death," Johannes Oldenburg, of the Universitatsklinikum Bonn, and colleagues reported in the *NEJM*.

Safety is paramount in this indication and patients are cautious about trying new therapies. Shire, which is the market leader in hemophilia, announced on July 9 that it obtained a preliminary injunction against Roche, charging that the company made misleading statements about adverse events in the HAVEN 1 study. The company also is looking to correct Roche's statements about primary efficacy results.

"Shire believes Roche has unlawfully disparaged Shire's proven bypassing agent, FEIBA (Anti-Inhibitor Coagulant Complex). Shire has issued multiple unheeded requests to Roche in an effort to resolve these concerns in an appropriate manner. As a result, Shire made the decision to seek court intervention," the company said in a statement.

NO NEW SAFETY SIGNALS

Roche reported that the serious adverse event rate in the HAVEN 1 study was 8.7%, with effects including injection site reactions, headache, upper respiratory infection and joint pain.

There were two cases of thromboembolic events and three TMA adverse events in the trial. Roche noted in a statement that patients who experienced these events had "more than 100 u/kg/day of the BPA activated prothrombin complex on average for 24 hours or more before the onset of the event." Two had also received recombinant Factor VIIa, the company reported.

"Roche management speculated that repeated dosing of FEIBA leads to an accumulation of Factor IX and Factor X, which are substrates for emicizumab … Roche management stated that they recognize the need for clear guidance around the use of emicizumab with FEIBA and they have included dosing guidance in their filings to regulators," Holford noted.

Holford said that the presentation of the HAVEN 1 study at the ISTH meeting and the publication of data in the *NEJM* confirmed the drug's "impressive efficacy profile and convenience that underpins our $5bn sales estimate."

Furthermore, and importantly, no new adverse events were reported and the drug is "highly unlikely to generate inhibitors," the analyst said.

"The data and discussion around the product also reassured us on the safety profile for emicizumab. (ACE910). Whilst approval risk, labeling, pricing and uptake may be heavily debated between now and the launch, we feel increasingly confident on its prospects," Holford wrote.

The HAVEN 1 study also had a positive reception in an *NEJM* editorial accompanying the study results. David Lillicrap of Queen's University in Ontario Canada said that the results are "extremely important for the hemophilia treatment community, which has battled the hemostatic calamity of Factor VIII inhibitor formation with the same bypassing therapies for the past 30 years."

"Emicizumab prophylaxis appears to offer a marked reduction in bleeding rates and improvement in quality of life for this very challenging patient group."

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Momentum Builds For Tomorrow's More Convenient Hemophilia Drugs

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The International Society on Thrombosis and Haemostasis (ISTH) Congress in Berlin provided a showcase for a new wave of hemophilia therapies to shine and advance – **Roche**'s bispecific antibody emicizumab and **Alnylam Pharmaceuticals Inc./Sanofi**'s RNA-interference therapy fitusiran as well as gene therapies from **BioMarin Pharmaceutical Inc.** and **Spark Therapeutics Inc.**

The ISTH meeting, held July 8-13, featured data for innovative therapies aspiring to compete with today's standard of care, including results from the Phase III HAVEN 1 and HAVEN 2 trials of Roche's emicizumab, which is under review with the US FDA and the European Medicines Association, and fitusiran, which just moved into Phase III. *(Also see "Phase III Updates Bode Well For Filings Of Roche's Emicizumab In Hemophilia" Scrip, 11 Jul, 2017.)*

Hemophilia typically is treated with repeated infusions, such as **Bioverativ Inc.**'s Factor VIII replacement *Eloctate* [antihemophilic Factor (recombinant)], which can be expensive as well as time-consuming. These infusions are also associated with development of inhibitors that make the disease resistant to treatment. Once inhibitors develop, patients move to bypassing agents like **Shire PLC's** prothrombin coagulant complex *FEIBA* and **Novo Nordisk AS**'s *NovoSeven*, which also are given by infusion at great expense.

Shire and Novo Nordisk are the market leaders in hemophilia with $3.7bn and DKK10.5bn ($1.5bn) in sales respectively for 2016, but are being challenged by new drugs that offer less frequent dosing and more convenient administration, though safety remains an important consideration.

Writing in a *New England Journal of Medicine* editorial on July 10 accompanying the HAVEN 1 results, David Lillicrap of Queen's University in Ontario, Canada, noted that for the last 50 years, treatment and prevention of bleeding for hemophilia A has involved intravenous infusion of plasma-derived or recombinant Factor VIII protein replacement.

"With an average half-life of 12 hours, these infusions have to be repeated several times each week to maintain protective levels of Factor VIII in the blood, and although recent bioengineering innovations have produced Factor VIII molecules with an average half-life of approximately 18 hours, more convenient treatment schedules are still being sought," Lillicrap said.

Emicizumab (ACE910) is a once-weekly, subcutaneously delivered therapy that binds to both Factor IXa and X. *(Also see "Roche's Emicizumab Progresses Against Hemophilia's Next Big Challenge: Patients With Factor VIII Inhibitors" Scrip, 18 Apr, 2017.)* Unlike Factor VIII replacement therapies, it has not been associated with development of Factor VIII inhibitors. It has initially been tested and filed for patients with inhibitors because Roche sees that as the area of greatest unmet need, but it also will be positioned for patients without inhibitors.

HAVEN 1 tested the drug in 109 patients aged 12 and up with hemophilia A who had developed inhibitors. The median treatment period in the trial was 24 weeks. The primary endpoint was the rate of bleeding for emicizumab prophylaxis versus no prophylaxis in patients who previously received episodic treatment with bypassing agents. Bypassing agents were given on demand for patients experiencing bleeding events in the trial. Those on emicizumab experienced a significantly lower rate of bleeding compared with the no prophylaxis group – an 87% reduction in risk of bleeding ($p<0.0001$) – and 63% in the test drug arm had zero bleeds vs. 6% in the comparator group.

HAVEN 1 also incorporated an analysis of patients who were previously assessed in a noninterventional study and received standard-of-care prophylaxis with bypassing agents.

Gallia Levy, associate group medical director at Roche's **Genentech Inc.**, explained that bleeding varies a lot from patient to patient, so it is helpful to know how well an individual would do with or without prophylactic emicizumab treatment. Recording of bleeding is subjective and inconsistent, so medical records are not useful in making this comparison.

The HAVEN 1 analysis provided a before-and-after picture for a subset of patients – in this group, the bleeding rate in the Phase III study was 79% lower ($p<0.001$) compared to how the same patients performed in the prior noninterventional trial.

Levy sees this result as one of the most important outcomes in the study.

"Those are incredibly powerful data that we would not have been able to get without having done the noninterventional study first," Levy told *Scrip*.

Emicizumab efficacy has impressed, but there have been concerns about reports of thrombotic microangiopathy, which caused a death in the trial.

TMA occurred in patients also getting treated concomitantly with FEIBA.

"Although the preferred treatment of the infrequent events of breakthrough bleeding during the administration of emicizumab is not clear, it is obvious that repeated high doses of activated prothrombin complex concentrate should be avoided," Lillicrap said in his editorial.

Roche believes that it can guard against the development of this adverse event through clear dosing guidance to regulators.

Roche also presented data from the single arm HAVEN 2 study in children under age 12 with hemophilia A and inhibitors at the ISTH meeting, noting that the data were consistent with the results in HAVEN 1. The study tested the drug over a 12-week treatment period in 19 pediatric patients.

One patient in the study had a bleed reported in the trial, but no joint or muscle bleeds were reported. In a subset of eight patients who had been enrolled in a noninterventional trial, there was a 100% reduction in treated bleeds.

The most common adverse events were mild injection-site reactions and cold; no thrombotic events or cases of thrombotic microangiopathy were reported.

"These are extraordinary times for innovation in hemophilia therapy and the

introduction of emicizumab represents a major contribution toward achieving an enhanced standard of care for this lifelong bleeding disorder," Lillicrap concluded in his *NEJM* editorial.

Writing in a July 10 note, Jefferies analyst Jeffrey Holford said that the data reported by Roche at the meeting and in the *NEJM* were impressive and reassuring on safety and support a sales projection of $5bn.

Two Phase III studies involving other dosing regimens and including patients without inhibitors – HAVEN 3 and HAVEN 4 – are ongoing. Levy said the company's vision is to have three dosing regimens available – weekly, every other week and monthly – to allow patients the greatest flexibility.

ALNYLAM'S MONTHLY FITUSIRAN MOVES TO PHASE III

Alnylam and Sanofi also are developing a monthly option via fitusiran, which reduces antithrombin as a way of improving clotting, to treat both hemophilia A and B, with and without inhibitors *(Also see "Alnylam's Fitusiran Could Provide Comprehensive Hemophilia Therapy Option" Scrip, 29 Aug, 2016.)*

The sponsors announced on July 7 that they have started the Phase III ATLAS program of fitusiran, having selected an 80 mg dose. The program consists of three Phase III studies in a total of 250 patients at 100 sites with hemophilia A and B with or without inhibitors and receiving prophylactic therapy. In all three studies, the primary endpoint is the reduction in the annualized bleeding rate and secondary endpoints include other bleeding measures and improvement in quality of life. Top-line data are expected in the second half of 2019.

Results from a Phase I study of hemophilia A and B were presented at the ISTH meeting on July 10 and published by John Pasi of the Royal London Hospital Barts Health NHS Trust in the *NEJM* the same day. Sponsors also released updated data from the Phase II OLE study at the meeting.

The Phase I study reported in the *NEJM* was an open-label escalation study that included four volunteers and 25 patients with moderate or severe hemophilia A or B but no inhibitor antibodies.

Investigators reported a dose-dependent antithrombin reduction ranging from 70% to 80% over baseline.

"In a post hoc exploratory analysis to determine the effect of monthly fitusiran administration on bleeding rates, there were fewer bleeding episodes per month after treatment with fitusiran than before treatment, a finding that was consistent with the reduction in antithrombin levels," Pasi and colleagues reported.

The data suggest that long-term fitusiran treatment "may allow for the functional conversion of severe hemophilia to a milder clinical phenotype," Pasi reported.

Adverse events included injection-site pain and elevated liver enzyme levels. Investigators reported transient increases in liver aminotransferase values in nine of 25 participants (36%) that could be related to the study drug. Of the 25 patients in the study, 64% had a history of hepatitis C infection. Two severe adverse events were reported – reactivation of hepatitis C and viral pneumonia.

An extension study of the trial is now ongoing.

The Phase II OLE study tested a monthly dose of either 50 mg or 80 mg of fitusiran in 33 patients, most of whom had hemophilia A, with treatment lasting up to 20 months (the median was 11 months).

Investigators reported that antithrombin was lowered in 80% of participants, and this decline was associated with an increase in the generation of thrombin. The median annualized bleeding rate was one for all patients and 0 for a subset with inhibitors and 67% had no spontaneous bleeds.

In the OLE study, about half of the non-inhibitor patients were on the lower dose and the annualized bleeding rate could move closer to 0 in Phase III with all patients on the higher dose, BMO Capital Markets analyst Do Kim commented in a July 10 note.

The companies reported that the drug was generally well-tolerated and adverse events included injection-site reactions in 18% of patients. Elevation of liver enzymes was an issue in the study and caused one patient who had hepatitis C virus (HCV) to drop out. There also was a serious case of seizure in one patient who had a history of seizure disorder.

Investigators also reported asymptomatic increases in alanine aminotransferase (ALT) liver enzymes more than three times the upper limit of normal in 11 patients who also had hepatitis C, but most of the cases resolved.

Of three patients who needed a dose interruption or to stop treatment, "all had active HCV, which likely contributed to the increase in ALT," and the others had prior or existing HCV infections, Kim noted. The sponsors plan to exclude patients with active HCV from the Phase III program, but will include those who have received curative treatment for the disease. The company said during a July 10 investor call that it anticipates minimal impact to its Phase III plans from this exclusion.

No thrombotic events were reported and bleeding events were successfully managed with Factor VIII, Factor IX or bypassing agents.

'AN ADVANTAGE OVER EMICIZUMAB'

Jefferies analyst Murray Raycroft said in a July 10 note that the lack of complications for patients who had bleeding episodes and took Factor VIII replacement or bypassing agents represents an advantage over Roche's emicizumab.

Alnylam CEO John Maraganore said during the company's investor call that the company is "very pleased" with efficacy and safety achieved in the study.

"Related to these results, it's important to note that the median duration of time in the OLE now exceeds the typical time period in Phase III trials for replacement factors and for agents in development, including the duration of time planned in our ATLAS trials. So we are even further encouraged about fitusiran's potential to provide meaningful hemostasis for patients," Maraganore said.

Raycroft concluded that the Phase I and II data presented at the ISTH meeting support "broad use in all types of adult hemophilia patients" and that the plan to exclude HCV patients should "successfully mitigate safety issues."

Though fitusiran is behind emicizumab, the approach is "differentiated and well-positioned," with superior dosing, Raycroft said.

Jefferies forecast $1bn in peak sales for fitusiran.

However, on July 10, the day the data were released at the ISTH meeting, Alnylam closed down 5.6% at $79.41.

Credit Suisse analyst Alethia Young said in a same-day note that the Alnylam stock weakness was due to the strong performance of Roche's emicizumab. Young noted, however, that there is room for more than one subcutaneous therapy for patients with inhibitors, though fitusiran will have a "real commercial battle" with emicizumab, which is getting to the market possibly two

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years earlier in those patients. The market for patients without inhibitors remains open to many players, the analyst said.

GENE THERAPY: ONE AND DONE

A handful of gene therapies also are in development for hemophilia and are aiming for a cure. BioMarin presented data on July 11 at the ISTH meeting from a Phase I/II study of its AAV-Factor VIII vector gene therapy BMN 270, which is designed as a one-time treatment for restoring Factor VIII plasma concentrations to normal levels in hemophilia A.

The company also confirmed it is moving forward in the fourth quarter with a Phase IIII registrational study for a higher dose than was tested in the Phase I/II trial – 6e13 vg/kg – in patients with hemophilia A and no inhibitors.

BioMarin is considering a study of 100 patients who will be given a single dose of BMN 270, with data collection lasting one year, and with long-term follow-up. Jefferies analyst Eun Yang expects that Phase III data could be available in mid-2019, with potential FDA approval by the end of 2019.

BioMarin's open-label study tested two different doses – 6e13 vg/kg or 4e13 vg/kg (each given as a single treatment) – in 15 patients with severe hemophilia A, defined as less than 1% expression of normal Factor VIII expression levels.

Five out of seven patients on the higher dose had normalized Factor VIII levels, defined as being in the range from 50% to 150%, that proved durable for 52 weeks. One patient had a level below 50% and one was above 150%. Going above 150% raises the risk for thrombosis.

In six patients on the high dose who had pre-study prophylaxis, the median annualized bleeding rate was reduced from 16.5 to zero and the mean number of annualized Factor VIII infusions was reduced by 94% from 16.5 to 0, BioMarin reported.

The company said the results suggest the gene therapy can shift severe hemophilia A patients to the normal range of Factor VIII expression "consistent with someone who has no disease."

Getting patients into the normal range will eliminate bleeds and the need for Factor VIII infusions, Henry Fuchs, president of worldwide research and development, said during a July 11 investor call.

"Treating with BMN 270 has the potential to revolutionize the way hemophilia A patients currently manage their disease. A one-time dose of BMN 270 has the potential to free severe hemophilia A patients from the distress and limitations of multiple, weekly recombinant Factor VIII infusions to manage their daily Factor VIII peaks and troughs," the exec said.

The lower dose helped patients get into the mild range of hemophilia and reduce bleeding and the need for infusions dramatically, but the company suggested that the hemophilia community prefers to see patients getting into the normal range and that the risk for thrombosis associated with the higher dose is low and manageable. However, BioMarin may still explore the lower dose in another study as this could provide another treatment option for patients. Those more concerned about the risk for thrombosis if Factor VIII goes too high, for example, might prefer a lower dose.

Fuchs said the company recognizes "that one size doesn't always fit all," but is aiming to get the higher dose registered "as quickly as possible."

The therapy was well-tolerated in the study, with adverse events including ALT elevations, which occurred in 67% of patients (none serious), arthralgia (47%) and back pain (33%).

The company said it will want to watch liver function tests as BMN 270 goes forward in Phase III. In the study reported at the ISTH meeting, the liver function abnormalities reversed and the Factor VIII level didn't decrease during that degree of liver inflammation, the Medical College of Wisconsin's Gilbert White noted during BioMarin's investor call.

"Usually, the reason the factor level decreases with liver function abnormalities is because liver cells are being killed. In this case, there's no evidence that liver cells are being killed. They just look like they're being inflamed and they keep producing the Factor VIII and then they become uninflamed and keep producing the Factor VIII," said White, who is director of the Blood Research Institute at the Blood Center of Wisconsin.

Analyst questions during the call included a query about how BMN 270 compares to emicizumab, given the enthusiasm for the latter drug at the ISTH meeting.

Amit Nathwani, professor of hematology at University College London, acknowledged the "huge amount of enthusiasm" for emicizumab, particularly in patients with inhibitors, but noted that the drug still requires repeated administration of product and that it is associated with significant toxicity.

"Gene therapy, in contrast, is a single administration that leads to long-term, stable expression. As I've mentioned before, at least in the hemophilia B studies, we see experiences last for seven years and still counting. There's absolutely no reason why the same should not happen for hemophilia A and other AAV-mediated gene transfer approaches. So that is a big difference for the patients. It actually liberates them from being tied to regular administration of product, which is something that they don't want," Nathwani said.

SPARK'S LONG-LASTING EFFECTS

Spark Therapeutics provided an update for its AAV-vector Factor IX gene therapy SPK-9001, which is partnered with **Pfizer Inc.**, in a Phase I/II hemophilia B study at the ISTH meeting. The data included results for one patient followed for 18 months and four who were followed for a year after a single infusion of SPK-9001.

In 10 patients studied overall, the annual infusion rate was reduced by 99% to a mean of one versus 67.5 annual infusions prior to administration, while the annualized bleeding rate was reduced by 96% to a mean of 0.4 annual bleeds, Spark reported on July 10.

No serious adverse events and no thrombotic events were reported. There was an issue with asymptomatic transient elevation of liver enzymes and cases were treated successfully with corticosteroids.

"All 10 trial participants have shown consistent and sustained increases in Factor IX activity level and a discontinuation of routine infusions of Factor IX concentrates," the company said in a statement.

BMO Capital Markets analyst Matthew Luchini commented in a July 10 note that the data were "consistent with prior updates and [we] believe they provide further evidence of a durable response."

The gene therapy provides proof-of-concept for the company's platform, but it is not as commercially relevant because it is partnered with Pfizer and it is being developed for the smaller hemophilia B market, the analyst said.

"Thus, we remain focused on SPK-8011 for the treatment of hemophilia A, where initial data are expected in July/August," Luchini said.

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Arena Rises, But Raises Questions With Phase II Ralinepag Data In PAH

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Arena Pharmaceuticals Inc.'s pulmonary arterial hypertension (PAH) drug candidate ralinepag met the efficacy bar that the company set for its oral therapy in a Phase II placebo-controlled study, but baseline characteristics of patients in the two treatment arms raise questions about what drove the results.

Investors liked what they saw when Arena released the highly-anticipated top-line data – the first Phase II efficacy results for one of two lead drugs under the company's new strategy, which represented a shift in focus from approved obesity therapy *Belviq* (lorcaserin) to ralinepag (APD811) and other early clinical-stage programs. Arena shot up 41.3% in after-hours trading on July 10 to $26.50 per share after the company said PAH patients treated with its selective agonist of the prostacyclin receptor had a statistically significant reduction in pulmonary vascular resistance (PVR) compared with placebo.

PVR changes and six-minute walk distance (6MWD) results were co-primary endpoints in the 61-patient Phase II study, in which patients were randomized 2:1 to ralinepag and placebo. Arena CEO Amit Munshi told *Scrip* that the trial was not powered to show a statistically significant difference between ralinepag and placebo in terms of the 6MWD, but he said the improvement from baseline was "clinically significant" for the company's drug.

"We're very pleased with the data and the conduct of the study and we think we're headed down a positive path," Munshi said.

Arena reported that ralinepag reduced median PVR by 163.9 dyn.s.cm-5 from baseline compared to a 0.7 dyn.s.cm-5 increase from baseline in the placebo arm at the end of the 22-week treatment period (p=0.02). The 20.1% improvement for ralinepag-treated patients versus baseline came in at the high end of the 15% to 20% gain that the company was hoping to reach based on feedback from physicians about what would be a significant result.

PVR had farther to fall for the ralinepag-treated patients, however, as chief medical officer Preston Klassen shared baseline patient population characteristics during the company's conference call that showed median PVR was much higher in the ralinepag treatment group versus the placebo group – 705 versus 480 dyn.s.cm-5. Even so, median PVR at 22 weeks improved by 29.8% when comparing ralinepag-treated patients with the placebo arm based on a least square means analysis (p=0.03).

"These Phase II data for oral ralinepag were supportive of further study, with a good improvement in PVR, though the data on 6MWD was confounded by a large increase in the placebo group," the Informa Pharma Intelligence service Biomedtracker noted in a July 10 report.

SMALL DIFFERENCE VERSUS PLACEBO ON 6MWD

The 6MWD results revealed during Arena's conference call showed that ralinepag-treated patients gained a mean of 36.2m versus their baseline performance while patients in the placebo group gained a mean of 29.4m from baseline for a difference of 6.8m. Mean total distances at baseline were 393m in the ralinepag group versus 351m in the placebo arm.

The ralinepag result versus baseline was statistically significant, but the placebo group's performance versus baseline and the 6MWD gains for ralinepag versus placebo were not significant. However, individuals in the placebo group may have benefited from recent changes in their background medicines. At baseline, 38% in the placebo group changed their background therapy within six months of initiating treatment in the Phase II study versus 12.5% in the ralinepag group.

It's also worth noting that ralinepag patients were more heavily medicated, since 48% of placebo patients were on a combination therapy regimen, while 65% in the ralinepag group took more than one background drug. In practice, most PAH patients are treated with a combination of drugs.

Side effects in the Phase II ralinepag study were described as "consistent with other prostacyclin treatments for the management of PAH, with headache, nausea, diarrhea, jaw pain and flushing being the most commonly reported adverse events." The events were more frequent in the nine-week dose titration period than during the 13-week stable treatment period.

Klassen noted during Arena's conference call that 12.5% of ralinepag-treated patients discontinued the study during the 25-week safety assessment period due to adverse events compared with 10% in the placebo group. However, only four patients (10%) in the ralinepag arm experienced a serious adverse event versus six (28.6%) placebo-treated patients. There were two deaths during the Phase II study, both of which occurred in the placebo arm.

Munshi declined to say in an interview whether the single incidence of transient atrial fibrillation seen in a Phase Ia study was repeated in the Phase II trial, but noted that "we're not seeing anything that makes us concerned at all." More detailed safety and efficacy data will be presented at a medical meeting either later this year or in 2018.

EFFICACY SIMILAR TO OTHER PROSTACYCLIN DRUGS?

Klassen praised the Phase II study in a statement from Arena for showing that ralinepag could be the first oral prostacyclin therapy to show efficacy similar to what is seen with intravenous prostacyclin receptor agonists. "These data give us confidence to move expeditiously toward a Phase III clinical program," the CMO noted.

The company will not provide details about its Phase III trial design until it speaks with the US FDA and the European Medicines Agency (EMA) about the Phase II results and the potential Phase III program, Munshi told *Scrip*. However, he noted that the regulators probably will only require one Phase III study, since that is what was required for other PAH drugs, including the only approved oral prostacyclin agonist *Uptravi* (selexipag) from **Actelion Pharmaceuticals Ltd.**, which **Johnson & Johnson** recently acquired for $30bn.

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While Munshi said "PVR is a strong proxy for being able to show you're affecting the underlying disease," he explained that Phase III PAH trials generally use 6MWD and clinical outcomes as primary and secondary endpoints. Testing for PVR requires the insertion of a catheter into the right side of the heart – a procedure that's difficult to do in a large clinical trial. However, the Phase II PVR and 6MWD results give Arena "a very good sense of how to design Phase III," Munshi said.

PAH is a rare and progressive disorder characterized by increased pressure in the arteries that carry blood from the heart to the lungs, which strains the heart, eventually leading to heart failure and reduced life expectancy. The disease primarily is treated with four types of drugs: endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, prostacyclin analogues and soluble guanylate cyclase (SGc) stimulators.

If Arena's Phase II results are repeated in Phase III, the company's oral drug will compete against well-established blockbuster PAH drug portfolios from **United Therapeutics Corp.** and Johnson & Johnson, including Actelion's oral Uptravi, which was approved at the end of 2015.

While Uptravi is a twice-daily pill and Arena tested twice-daily ralinepag in its Phase II study, the company hopes to move forward with an extended-release formulation in Phase III that will allow for once-daily dosing. However, Leerink analyst Joseph Schwartz noted in a June 6 report that **GlaxoSmithKline PLC**'s long-generic intravenous drug *Flolan* (epoprostenol sodium) "is still considered the gold standard for efficacy in PAH."

Biomedtracker noted in a July 10 analysis that "Ralinepag had a reduction in PVR versus placebo of 25.8% using a geometric mean ratio (used as the data was not normally distributed) and 29.8% using a least square means method. For comparison, oral Uptravi had a geometric mean reduction of 33% in its Phase II study (per an FDA review and publication) and IV Flolan had a mean improvement of 30% [in Phase II]. The results could be quite variable given the small size of these studies, so it is difficult to make much of the differences. For example, patients in the Flolan and Uptravi studies started with higher PVR levels than those in the ralinepag trial."

Biomedtracker concluded that, "All in all, the PVR data suggest ralinepag could have at least similar efficacy to other agents in the class, though differences in the baseline characteristics of the treatment groups and lack of a benefit versus placebo on the 6MWD cloud the picture somewhat."

Phase III efficacy establishing ralinepag as a best-in-class oral prostacyclin agonist with similar efficacy to IV prostacyclin-targeting therapies could make Arena's drug a blockbuster product, JMP Securities analyst Jason Butler said in a July 7 report to help investors evaluate the Phase II results that were expected this month.

"In our view, addressing selexipag's suboptimal efficacy, and being better positioned to demonstrate a mortality benefit in Phase III development, while still providing the convenience of an oral therapy, would support a multibillion-dollar product opportunity," Butler wrote, pointing to ralinepag's superior preclinical pharmacology results compared with Uptravi.

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Inotek's Options After Another Glaucoma Failure

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Inotek Pharmaceuticals Corp. is evaluating its strategic alternatives after top-line data from a Phase II study showed that its investigational glaucoma product trabodenoson had no added benefit when used as part of a fixed-dose combination with latanoprost compared with the older therapy alone.

Trabodenoson had already disappointed in a Phase III monotherapy trial in January (MATrX-1), but at the time Inotek stressed that its ambitions for the product really lay with the latanoprost combination. Its failure here has really sounded the drug's death knell in glaucoma, and left the company in limbo. Inotek's share price fell 48% to $0.90 when NASDAQ opened on 10 July.

But Inotek is not without funds: it had an estimated $108.7m in cash and marketable securities as of the end of the second quarter of 2017. The company has engaged a financial advisor, Perella Weinberg Partners, to assist with the strategic review, although it could not guarantee that a transaction would result. It will also not disclose any additional details "unless and until it has entered into a specific transaction or otherwise determines that further disclosure is appropriate".

"We will continue to streamline our operations to preserve cash for value-creating opportunities," Inotek president and CEO David P. Southwell said during a conference call.

He added that the strategic review would also consider options for Inotek's preclinical assets, namely trabodenoson in other eye diseases. The company has previously said that trabodenoson had demonstrated preclinical activity in ophthalmic indications where there is high unmet need, including nonarteritic ischemic optic neuropathies (better known as NAION), the leading cause of sudden vision loss. "We also have intriguing data demonstrating the potential for neuroenhancement," Southwell said.

The 201-patient Phase II trial showed that while trabodenoson/latanoprost showed some benefit over latonoprost after four weeks of a once daily morning dose, this benefit disappeared after an additional four weeks of a once-daily evening dose.

When dosed in the morning and examined on Day 28, the trabodenoson 3%/latanoprost 0.005% combination showed 1.2 mmHg additivity to commercial latanoprost. However, by Day 56, while the IOP lowering effect of latanoprost improved by 1.3 mmHg, the fixed dose combination of trabodenoson/latanoprost remained unchanged.

Overall, the addition of trabodenoson to latanoprost offered no clinically meaningful advantage in eye pressure reduction over latanoprost alone, Southwell admitted.

The setback for Inotek removes some pressure on rival company **Aerie Pharmaceuticals Inc.**, which has a netasurdil/latanoprost combination product (*Rocklatan*) that succeeded in two Phase III trials and is due to be filed for US approval in the first half of 2018.

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Iterum Therapeutics Focused On First Oral Penem

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Dublin, Ireland and Chicago, Illinois-based **Iterum Therapeutics Ltd.**, set up in 2015 by a small team of biotech executives and a VC syndicate, has in its sights the development of the first penem antibiotic that can be administered orally, sulopenem.

The compound can also be administered intravenously and has a broad spectrum of activity, making it potentially useful for both hospital- and community-based treatment of bacterial infections, and in particular Gram-negative, multi-drug resistant infections.

"Our strategy is to acquire assets that we think are important and can satisfy a medical need, and we knew about this particular asset, sulopenem that had been studied at **Pfizer Inc.**, and so we acquired it from the big pharma," said Iterum's CEO Corey Fishman in an interview.

Urinary tract infections (UTIs) are to be targeted by sulopenem

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Company Name: Iterum Therapeutics Ltd.
Location: Dublin, Ireland and Chicago, Illinois, US
R&D Focus: oral penem antibiotics
Disease Area: antibacterials
Founding Date: 2015
Founders: Corey Fishman, Michael Dunne, Judith Matthews and others not disclosed.
Financing To Date: $105m in Series A and B.
Investors: Advent Life Sciences, Arix Bioscience PLC, Bay City Capital, Canaan Partners, Domain Associates, Frazier Healthcare Partners, New Leaf Venture Partners, Pivotal Bioventure Partners, Sofinnova Ventures.

It was not so much pulling an asset off the shelf of big pharma, it was more a case of identifying the medical need and then finding something to satisfy that need, Fishman noted. The R&D pipeline at Pfizer has been in constant flux over recent years, with anti-infectives falling out of favor, and sulopenem appears to be a compound that became marooned at an early clinical development stage.

The group of colleagues involved in setting up Iterum mostly worked together at **Durata Therapeutics Inc.**, the Chicago-based company that took the antibiotic, *Dalvance* (dalbavancin) through development and approval in the US and Europe, before that company was acquired by **Actavis** (now **Allergan PLC)** in October 2014 in a deal worth more than $800m. *(Also see "Actavis builds antibiotic presence with $675m+ Durata deal" Scrip, 7 Oct, 2014.)*

"We really enjoyed the experience of bringing a product to market for an important medical need, and we liked working with each other, and we would like to do it again," remarked Fishman.

Fishman was previously CFO and COO at Durata, and is joined in Iterum with co-founder Michael Dunne, who was chief medical officer at Durata until 214, and is now chief scientific officer of Iterum. Other ex-Durata appointments at Iterum include Judith Matthews as chief financial officer and Benjamin Pe as vice president of operations.

To support their work, Iterum raised $65m in a series B financing in May 2017, led by new investor Arix Bioscience plc and including Pivotal bioVenture Partners, Advent Life Sciences, Domain Associates and Bay City Capital. *(Also see "Venture Funding Deals: $65m For Iterum's Antibiotic; Genoa's IPF Drug Nets $62m" Scrip, 9 Jun, 2017.)*

All of its current investors also participated in the round: Frazier Healthcare Partners, Canaan Partners, Sofinnova Ventures and New Leaf Venture Partners. In the Series A round, completed in March 2016, Iterum raised $40m. *(Also see "UK Firms Lead As EU Biotechs Complete Best Ever 1Q VC Fundraising" Scrip, 4 Apr, 2016.)*

A significant amount of preclinical and early clinical work has already been done by Pfizer on sulopenem, and Iterum intends to build on that work. The potential market opportunity for sulopenem, according to Fishman, includes its use as a step-down agent in patients hospitalized with serious infections, and also in patients in the community, in an indication like uncomplicated urinary tract infections, where there has not been a new agent for nearly two decades, and physicians are running out of options to tackle growing bacterial resistance.

"We are in the planning stage for three Phase III studies to begin in the first half of 2018," Fishman reported. These will each cover one indication: either complicated urinary tract infections, uncomplicated urinary tract infections, or complicated intra-abdominal infections. Iterum wants to try and identify patient types and geographies that would preferentially benefit from sulopenem therapy. Oral quinolones are often used for UTIs and as step-down agents, but bacteria are becoming more and more resistant to these drugs, he added. A US NDA filing is expected by year-end 2019.

In the US, Iterum will evaluate commercializing sulopenem itself and may require additional fundraising, but Fishman is keen to build a robust anti-infectives company, and is also looking for assets that could complement sulopenem, and for partners that that could commercialize the product outside of the US.

Iterum is currently spread across several locations: the headquarters are in Dublin, Ireland and some regulatory and medical staff will likely be housed there. The company also has a clinical development laboratory in Connecticut, and a small commercial and corporate team in Chicago, Illinois.

From the editors of Start-Up.
Published online 12 July 2017

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.

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Selected clinical trial developments for the week 7–13 July 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Boehringer Ingelheim GMBH	*Praxbind* (idarucizumab)	anticoagulation reversal for Pradaxa in emergencies	RE-VERSE AD; *NEJM* online, July 11, 2017.
Roche	emicizumab	hemophilia A	HAVEN 1; the *NEJM* online, July 10, 2017.
Teva Pharmaceutical Industries Ltd.	*Austedo* (deutetrabenazine)	Huntington's disease	ARC-HD; *JAMA Neurology* online, July 10 2017.
Updated Phase III Results			
Swedish Orphan Biovitrum AB / Bioverativ Inc.	*Eloctate* (efmoroctocog alfa)	hemophilia A	ASPIRE; safe and effective in Europe subgroup.
CSL Behring	*Idelvion* (albutrepenonacog alfa)	hemophilia B	PROLONG, Children; high FIX activity, improved quality of life.
Swedish Orphan Biovitrum AB/ Bioverativ Inc.	*Alprolix* (eftrenonacog alfa)	hemophilia B	B-YOND; reduced joint bleeds.
Bayer AG/Johnson & Johnson	*Xarelto* (rivaroxaban)	venous thromboembolism	EINSTEIN CHOICE; benefits shown with extended use.
Ionis Pharmaceuticals Inc./ GlaxoSmithKline PLC	inotersen	familial amyloid polyneuropathy	NEURO-TTR; clinical benefits shown.
ProMetic Life Sciences Inc.	*Ryplazim* (plasminogen, human purified)	hypoplasminogenemia	Effective with no safety concerns.
Novan Inc.	SB204 (nitric oxide releasing gel)	acne	Reduced inflamed and non-inflamed lesions.
Portola Pharmaceuticals Inc.	*Andexxa* (andexanet alfa)	anticoagulation reversal	ANNEXA-4; model predicted extent of benefit.
Phase III Completed			
Amgen Inc.	*Kyprolis* (carfilzomib) plus lenalidomide and dexamethasone	multiple myeloma	ASPIRE; improved overall survival in second Phase III study.
Phase III Interim/Top-line Results			
Bio Products Labs	*Coagudex* (coagulation Factor X, human)	hereditary Factor X deficiency	TEN 02; reduces bleeding episodes in children less than 12 years old.
Phase III Initiated			
Bristol-Myers Squibb Co./ Exelixis Inc.	*Opdivo* (nivolumab) plus *Cabometyx* (cabozantinib) and *Yervoy* (ipilimumab)	renal cell cancer	CheckMate 9ER; versus sunitinib, PFS as primary endpoint.
AbbVie Inc. /Neurocrine Biosciences Inc.	elagolix	endometriosis-associated pain	M14-702; in patients with moderate to severe symptoms.
Sanofi/Alnylam Pharmaceuticals Inc.	fitusiran with or without inhibitors; an RNAi therapeutic	hemophilia A and B	ATLAS program; top-line results in mid- to late-2019.
Vifor Pharma Group/ Daiichi Sankyo Co. Ltd.	*Ferinject* (ferric carboxymaltose)	anemia	AFFIRM-AHF, FAIR-HF2, HEART-FID; on heart failure and iron deficiency morbidity outcomes.

Source: Biomedtracker

First Approval For Kolon's Invossa But No Disease-Modifying Status

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Kolon Life Science Inc. has earned its first regulatory approval for *Invossa*, the world's first allogeneic cell-mediated gene therapy for degenerative osteoarthritis (OA), in South Korea, after 19 years of development.

Invossa (TissueGene-C; tonogenchoncel-L) was approved as a treatment for serious OA of the knee (Kellgren & Lawrence grade 3) via a single intra-articular injection. The approval is South Korea's first gene therapy approval and the product is the country's 29th domestically developed novel therapy, said the Ministry of Food and Safety (MFDS) in a statement.

Although Invossa didn't get the disease-modifying status from the MFDS as hoped for, the company expects it to become a first-in-class OA drug with a new mechanism that can provide a promising alternative for patients who are not responsive to existing pain killers, or are suffering from the side effects of these.

Kolon plans to launch Invossa in South Korea this year through sister firm Kolon Pharma and Mundipharma Korea, and will begin to produce the product in its plant in Chungju in the country. The company also plans to begin reimbursement price negotiations with the Health Insurance Review & Assessment Service.

Kolon Life's stock, which is traded on the second-tier Kosdaq market, closed 15.8% lower to KRW147,200 ($128.8) on July 12 on disappointment over its failure to get the disease-modifying status. The MFDS said Invossa has confirmed safety and efficacy, but did not show a difference with the control group in structural improvement through MRI. Hanwha Investment & Securities noted in a research note July 13 that the latest approval by MFDS focused more on Invossa's efficacy as a new OA treatment rather than its cartilage regeneration effect. "The company plans to prove the drug's cartilage regeneration effect through further clinical trials in the US, so it is not a disappointing news," said Hanwha.

Invossa's approval came after its regulatory approval filing in July last year. "The latest achievement is the outcome of 19 years of persistent investment, efforts and waiting. Beyond Kolon Life's success, this will serve as the green light of South Korea's biotech industry," said Woo-Sok Lee, CEO of Kolon Life, in the statement.

Invossa is an allogeneic (donor) cell therapy involving human chondrocytes (cartilage cells) that have been genetically modified to produce the therapeutic growth factor TGF-beta1, which is said to induce cartilage regeneration in patients with osteoarthritis. It has the ability to relieve knee pain and improve knee function by not only treating arthritic symptoms but the underlying disease itself, unlike current drugs. Administered via intra-articular injection, without the need for anesthesia or surgical intervention, the therapy is said to control pain for a minimum of one to two years per injection.

(Editor's Note: Source data/analysis from Biomedtracker)

From the editors of *PharmAsia News*.

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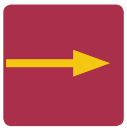

View market prospects here: **http://bit.ly/2uE98SF**

APPOINTMENTS

Pfizer Inc.'s former senior vice president of medicinal sciences, ***Tony Wood***, has been appointed **GlaxoSmithKline PLC.'s** senior vice president, platform technology and science, pharma R&D – effective October, 2017. ***John Baldoni***, who currently holds this role at GSK, will be leading a new team for the company in drug discovery.

GlaxoSmithKline PLC.'s former CEO, ***Sir Andrew Witty***, has been appointed to **G1 Therapeutics Inc.**'s board of directors. Witty is chancellor of the University of Nottingham and retired from GSK this year, after being at the company since 1985.

Francesco Maria Lavino has joined **Nabriva Therapeutics AG** as chief commercial officer from Merck & Co. Inc., where most recently he was assistant vice president, global brand leader anti-infective portfolio. Before this, he was vice president international marketing for the anti-infectives portfolio at Cubist Pharmaceuticals Inc.

Jesper Høiland has joined **Radius Health Inc.** as president and CEO and carries 30 years of experience in the biopharmaceutical industry, having previously held various senior leadership roles. Since 1987, Høiland was at Novo Nordisk Inc., and served in multiple roles of increasing responsibility, most recently as president of Novo Nordisk Inc. US.

Ferring Pharmaceuticals has promoted ***Lars Peter Brunse*** to executive vice president, chief production officer and member of Ferring's executive board. Brunse joined Ferring as associate director technical operations in 2000 and was later promoted to senior vice president, technical operations and logistics.

Ali Mortazavi, Silence Therapeutics Plc.'s CEO, has been named **Ultromics**' non-executive chair – effectively immediately. Ultromics is a technology that takes data points from one image and uses a form of artificial intelligence to determine which points are individual to a particular disease. This technology is currently being applied to echocardiograms to improve the diagnostic accuracy of coronary artery disease.

AcelRx Pharmaceuticals Inc. has appointed ***Raffi Asadorian*** chief financial officer (CFO) – effective August 16, 2017. Asadorian has more than 25 years' finance, strategy and corporate development experience and most recently, he was CFO at Amyris. Prior to Amyris, Asadorian was CFO for UniLabs and he started his career at PricewaterhouseCoopers (PwC).


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