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Shire Could Reclaim HAE Prophylaxis Market From CSL Behring

JOSEPH HAAS joseph.haas@informa.com

US FDA approval for **Shire PLC**'s *Takhzyro* as a subcutaneous prophylactic for attacks of hereditary angioedema should position the company to begin winning back market share lost to **CSL Behring**'s prophylactic agent *Haegarda*. Analysts predict rapidly ramping sales for Takhzyro, reaching blockbuster totals in just a few years.

Unlike Haegarda, which inhibits HAE patients' C1 esterase levels, Takhzyro (lanadelumab-flyo) is a kallikrein-inhibiting monoclonal antibody. It is the first antibody product approved for HAE – thought to affect roughly 40,000 patients globally – and the first prophylactic agent that addresses kallikrein, an enzyme that is chronically uncontrolled in HAE patients.

Shire's *Kalbitor* (ecallantide), approved in 2009, also is a kallikrein-inhibitor, but it is the lowest-selling of the firm's three HAE drugs. US sales totaled $48.3m in 2017, compared to $427.3m for *Cinryze*, a C1 esterase inhibitor approved for prophylaxis, and $229.7m for *Firazyr* (icatibant), a bradykinin B2 receptor inhibitor approved to treat acute HAE attacks.

The specialty pharma has conceded that following launch the antibody product might cannibalize its existing HAE portfolio. Analysts said in notes following the Aug. 23 Takhzyro approval that while this might happen, the drug's sales may eventually exceed what the other HAE therapies were earning and bring currently untreated patients into the fold due to its convenience of administration.

"Today's approval should position Shire to not only maintain but also significantly grow its dominant HAE franchise," Jefferies analyst David Steinberg wrote. He predicted that the product will be launched in the fourth quarter of 2018 and eventually achieve peak global sales of approximately $1.8bn.

Privately held CSL Behring does not divulge sales for individual products, but on Aug. 15 reported that sales of its specialty drugs, including Haegarda, totaled $1.49bn for the 12 months that ended June 30. It also claimed the product had taken roughly a 50% market share in the US for HAE prevention since its launch in 2017.

BROAD ADOPTION EXPECTED

Shire has not yet announced a launch date or pricing for Takhzyro. Shire Chief Medical Officer Howard Mayer asserted in an interview that the product may achieve "broad adoption given its product profile, certainly in patients with HAE who have considered prophylaxis in the past, but also patients who are receiving on-demand therapy."

In the 125-patient, Phase III HELP trial – the largest study conducted to date in HAE prevention, according to Shire – a 300 mg dose given every two weeks resulted in a mean monthly 87% reduction in attacks compared to placebo. The drug also met all secondary endpoints with no treatment-related serious adverse events. Of the patients receiving study drug who completed HELP, 97% continued into an open-label extension trial to evaluate long-term safety and efficacy of Takhzyro, Shire noted.

The secondary endpoints further underline the product's efficacy, Mayer said. At the end of six months, participants who

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

from the executive editor

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It's unfortunately trite to say that cardiovascular drug development takes a lot of heart, but it does require an amazing amount of dedication and consistency – not to mention resources. The recent European Society of Cardiology annual meeting underscored the long-term commitment required in this field.

Johnson & Johnson and Bayer's partnership on *Xarelto* is a prime example. Following up on the original pivotal trials, they set off on an ambitious plan to expand the novel oral anticoagulant's use with the EXPLORER trial program, with a target of over 100,000 patients across five trials. This was later expanded in high-risk populations with another 11 trials covering more than 275,000 patients – which the companies note is "unmatched" by any other NOAC in its size, scope and ambition. They are looking to add another 10 indications/label expansions to the six already approved in the US, and seek to deliver on that with the MARINER data presented at ESC.

As the article on p17 explores, while the COMMANDER HF study will not support a filing in heart failure, the companies believe they can seek approval in certain acutely medically ill patients based on the MARINER trial, in combination with the older MAGELLAN trial. The path forward shows the value of foresight and extensive data collection out of such a broad program.

Other highlights out of the ESC meeting include Pfizer's ATTR-ACT trial for tafamidis (p20). And check online for coverage of the CAMELLIA trial for Eisai/Arena's obesity drug *Belviq* – which leaves lingering questions.

Scrip

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Q&A: Merck KGaA Global Head Of Medical Affairs On Pipeline Persistence
https://bit.ly/2wu8cyZ

Maria Rivas has been in post as Merck KGaA's global head of medical affairs for just over a month. She talks to Scrip about her immediate priorities, and the Darmstadt-based company's potential in immunotherapies and oncology.

Anoro Comparisons Trip Up AZ's Bevespi In Latest COPD Study
https://bit.ly/2wlOi9N

AstraZeneca has failed to show that its LAMA/LABA combo Bevespi Aerosphere is better than GSK's Anoro Ellipta in a Phase IIIb study, a result "inconsistent" with previous data, but not surprising according to experts.

Chindia Generics: A Dream or Reality?
https://bit.ly/2MyjQn4

Meeting and greeting is necessary, as is the right form of partnership and getting everyone on board. But as Indian drug makers learn the ropes of entering the complex Chinese market, the seemingly natural fit may still have a long way to go.

Novo Nordisk Adds Momentum To Oral Semaglutide With Good PIONEER 5 Data
https://bit.ly/2wo4XcS

Novo Nordisk announced another set of positive PIONEER trial data backing its oral GLP-1 receptor agonist semaglutide, this time showing superior reduction of blood sugar levels and weight in adults with type 2 diabetes compared with placebo.

Pfizer, Astellas Accelerate Xtandi's Timeline In Early Prostate Cancer
https://bit.ly/2BK9Y4Q

Protocol changes for the Phase III ARCHES and EMBARK trials will deliver results in hormone-sensitive prostate cancer a year and a half earlier than expected. Xtandi may then gain a valuable new indication sooner than anticipated, but generics for competitor Zytiga could launch before then.

Deal Watch: Harbour Expands Horizons Beyond China
https://bit.ly/2BTxcFO

Antibody developer Harbour Biomed signs its first deal for rights outside China in cancer pact with Kelun. Portage buys SalvaRx to increase its immuno-oncology capabilities, while Paragon spinout Emalex will take over Psyadon's pediatric Tourette syndrome program.

inside:

China Vs. Cancer: Seven Companies Given Price Cuts, Roche Gets New Approval

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China's newly established Medical Insurance and Support Administration (MISA) has thrown its first punch, lowering the prices of 14 widely prescribed cancer drugs.

The majority of the products affected are from multinationals, which accounted for seven out of the nine companies hit by the new cuts.

The reductions ranged from 3% to 7.8%, with an average cut of 4.8%, and were based on new import tariffs and reductions in value-added tax (VAT). Since May, the Chinese government has reduced import tariffs for cancer drugs from 3-6% to zero, and lowered the effective VAT rate from 17% to 3%.

The affected products include **Johnson & Johnson**'s *Velcade* (bortezomib) and *Zytiga* (abiraterone); **Bayer AG**'s *Nexevar* (sorafenib), **AstraZeneca PLC**'s *Iressa* (gefitinib) and *Faslodex* (fulvestrant); **Novartis AG**'s *Afinitor* (everolimus); **Celgene Corp.**'s *Revlimid* (lenalidomide); **GlaxoSmithKline PLC**'s *Tykerb* (lapatinib) and **Roche**'s *MabThera* (rituximab), *Herceptin* (trastuzumab), *Tarceva* (erlotinib) and *Avastin* (bevacizumab). (Celgene has since licensed Revlimid to **BeiGene Ltd.** in China.)

Drugs from domestic makers hit by the move include **Betta Pharmaceuticals Co. Ltd.**'s *Conmana* (icotinib) and **Jiangsu Hengrui Medicine Co. Ltd.**'s *Aitan* (apatinib), which are also on the price reduction list.

Based on its new policies, MISA has initiated new negotiations with cancer drug makers, requiring them to comply with recalculated prices based on the new tariff/tax rate.

PREVIOUS CUTS

Some of the cancer drugs had already seen deep price cuts in a previous round of price negotiations, such as Iressa, Conmana and Tarceva. The first two were hit by the 2016 price negotiations, with Iressa cut by 55%, to CNY2,358 ($343.80) for a box of 10 x 250mg tablets, and Conmana suffered a 54% reduction to CNY1,399 per box of 21 x 125mg tablets. Roche backed out of that round, but voluntarily cut its prices for Tarceva later.

Since the wide success in China of the blockbuster movie *Dying to Survive*, which is about the problems of cancer drug access and has shed a harsh light on prices, the issue has become a national hot button topic.

> The new price reductions reflect an increasing pressure on makers to lower prices, even for some products still under patent protection

Chinese Premier Li Keqiang has repeatedly requested a lowering of oncology drug pricing, and the pressure is building for access to products that have not been covered by the National Drug Reimbursement List (NDRL). Dedicated price negotiations will start soon to further lower the burden to patients, noted the medical insurance agency.

OTHER DRUGS

The new price reductions reflect an increasing pressure on makers to lower prices, even for some products still under patent protection and for which there is no generic competition in China.

One tactic is volume in return for price reduction, under which manufacturers agree to cuts to ensure inclusion into the national medical insurance coverage scheme and the expected large volume uptake this should bring.

Novartis's *Lucentis* (ranibizumab), for one, was priced at CNY7,125 per 10mg/ml, 0.2ml vial in the first round of price negotiations to ensure inclusion in the NDRL in 2017, when the list was updated after an eight-year hiatus. After the negotiations, Lucentis was cut to CNY5,700 per vial, a reduction of 20%, the reasoning being that China's medical insurance scheme covers a wide population.

For cancer drugs that face generic competition in China, the prices may be cut more deeply. On August 3, the newly established MISA noted a new effort to cut levels for both originator drugs and generics.

During bidding discussions, MISA is said to have proposed using the lowest bidding price as the reference for both originator and generics drugs that have passed bioequivalence testing.

ALECENSA'S FAST APPROVAL

Parallel to the new price reductions, China meanwhile has been accelerating new cancer drug approvals. The latest such clearance has been granted to Roche's non-small cell lung cancer therapy *Alecensa* (alectinib). Developed by **Chugai Pharmaceutical Co. Ltd.** , this is indicated for anaplastic lymphoma kinase (ALK)-positive NSCLC patients.

Lung cancer is the most prevalent form of malignancy in China, with 80-85% of all patients having NSCLC; ALK-positive disease is a rare but fast-progressing type.

Alecensa gained US approval last November, and EU approval one month later. In March, the China FDA granted it a priority review and an official approval five months later.

To accelerate new oncology products to the market, China is using the priority review mechanism to shorten approvals to as little as six months, from 18-24 months previously.

In a rare and bold move, the country also recently released a list of 48 drugs from multinationals qualified for such fast-track reviews. *(Also see "China Calling: Dozens Of Drug Firms Handpicked For Fast Track Reviews" - Pink Sheet, 12 Aug, 2018.)*

Alecensa is the third drug from Roche to treat NSCLC in China, after Tarceva and Avastin.

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From the editors of PharmAsia News.

Portfolio Streamlining At GSK India But Long Term Commitment Intact

ANJU GHANGURDE anju.ghangurde@informa.com

GlaxoSmithKline PLC expects to prune the number of products it will focus on in India as the UK-based multinational tweaks its emerging markets business model with an eye on improved competitiveness and profitability. The effective roll out of innovative products on the Indian market will remain a thrust area.

GSK India will now focus on 20 key brands to drive growth in identified therapy areas over the next 18 months or so, down from around 70 brands currently. The firm is said to have, over the past, already pared the number of brands from about 130 to 70.

Fewer brands would help simplify operations and also allow the company to "put our energy where it matters", GSK India was reported as saying in the local media. The streamlining effort could also potentially see some brands being sold or discontinued, though there is no official word on this as yet.

GlaxoSmithKline Pharmaceuticals Ltd., the Indian arm of the multinational, is evolving its commercial operating model in India to invest resources in key products and patients/consumers to drive growth. Identified therapies will also be supported by an "incremental field force" during the course of the year, the Indian arm said at the time of its first quarter results on July 24.

COMMITTED TO INDIA

But no major pull back of sorts appears on the cards in India, and GSK emphasized to *Scrip* that the country is a "very important" market in which it has a "strong heritage and ambitious plans" for patient access to its world-leading medicines and vaccines.

"We are focusing on key brands to drive growth in identified therapy areas where there is significant unmet patient need. We are also increasing our field force by a third, and are committed to India and its patients for the long-term," the company added.

The main focus therapy areas will be anti-infectives, dermatology and vaccines – segments where GSK already has a leadership position in India – and also the respiratory space. GSK is the number one company in the vaccines self-pay segment in India with around a 28% market share in value terms.

The self-pay vaccines market in India is estimated at INR19.92bn ($285m) as per IMS MAT (moving annual total) data for March 2018, and growing at around 16%. Seven of GSK's products figure in the top 20 list of vaccines in the self-pay market, the data show.

GSK also expects to introduce in India innovative products from its global pipeline, especially in the anti-infectives and respiratory segment.

Scrip recently reported that novel respiratory products like *Nucala* (mepolizumab) and *Relvar Ellipta* (fluticasone/vilanterol), known as *Breo Ellipta* in the US, were among the new products headed to India from the global portfolio. *(Also see "Nucala Among Flurry Of New Respiratory Products On Indian Horizon" - Scrip, 7 Aug, 2018.)*

Much of the streamlining in India appears geared towards accelerating sustained profitable growth to create "enduring value" for shareholders.

"We will be driving this performance with fewer but more focused priorities," Annaswamy Vaidheesh, GlaxoSmithKline Pharmaceuticals' vice president South Asia and managing director India, said in the company's latest annual report.

He maintained this will help the company become "more competitive, win in the market", and serve patients, while the approach is also strongly aligned with the long-term priorities – Innovation, Performance and Trust – as laid out by GSK's CEO Emma Walmsley.

Last year, Walmsley had, among other aspects, emphasized the need to be more competitive in emerging markets, where returns in some cases had been impacted by competition and evolving regulations.

"We need a model that can competitively drive what is today a largely classic branded product business with brands like *Augmentin* (amoxicillin/clavulanate), but also one that can successfully launch more new innovations such as the Ellipta portfolio or Nucala. To do this we are going to create a new, single, dedicated, end-to-end operating model for emerging markets spanning commercial, supply and R&D for life-cycle management," Walmsley said at the time.

The group was expected to develop its own dedicated governance model and the "right commercial structure" for each market, whether this be a standalone business, a cluster of similar markets, or a distributor-led model. Each market will be resourced accordingly and the company remains very committed to access to its medicines, Walmsley said at the time.

INDIA MARKET PRESSURES

GSK's tweaked avatar in India, though part of a broader emerging markets revamp at the company, also comes against the backdrop of multiple market pressures in the country, including sustained efforts to cap prices of essential medicines, a push towards generic name prescriptions, and evolving clinical trial regulations. *(Also see "OPPI Chief Vaidheesh On Burning Industry Issues In India" - , 4 Dec, 2017.)*

Once the top ranked company in India, GSK is currently at ninth position in the country as per July 2018 MAT data from AIOCD AWACS, a market research agency that tracks retail sales. The British multinational has, however, already been fine-tuning its operations in the country to propel growth.

In 2016, GSK India boss Vaidheesh told *Scrip* how the firm was deploying a host of measures including cross functional "excellence teams", a multi-channel approach to reduce "information asymmetry" for customers, calibrating prices to improve access, and penetrating deeper into middle and rural India as part of efforts to create, deliver and capture value.

It is not immediately clear if some of these plans may have been further tweaked under the emerging markets remodeling effort.

Published online 23 August 2018

PATENT LOSSES CHARACTERIZE JAPAN'S CHALLENGING PHARMA FUTURE

COMPANY GROWTH

$69.5bn
Total predicted revenues **by 2027**

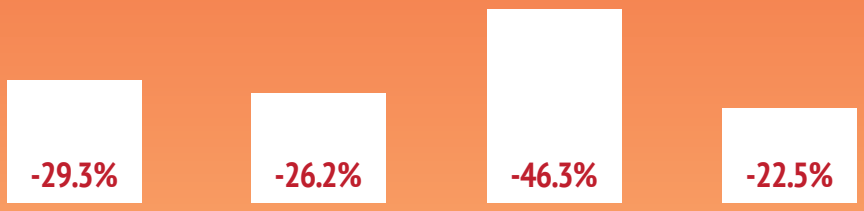
$11.4bn
Revenues from new drugs added by just **10 companies**

2018: **48.8%**
2027: **46.3%**
Share of the native market drops due to presence of foreign companies

GENERIC COMPETITION

$4.4bn
wiped from core and expiry portfolios

LOSSES



Astellas marketed drugs portfolio

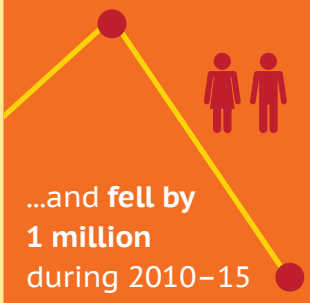
Daiichi Sankyo marketed drugs portfolio

Kyowa Hakko Kirin current marketed portfolio values

Sumitomo Dainippon current marketed portfolio values

OPERATING ENVIRONMENT

Population peaked in 2009...



...and **fell by 1 million** during 2010–15

33% of population was **over 60** in 2015

42.4% will be aged **over 60** in 2050

Target generic volume share of **80%** of substitutable market

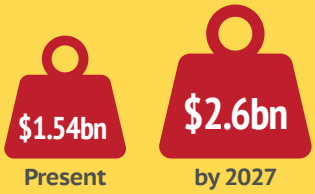
More drug price cuts will come in 2020

Although 10 of Japan's largest pharma companies look set to add $11bn in revenues over the next nine years, a CAGR of only 1% reflects an expected $4.8bn in patent expiries, leaving Japanese pharma heads relying on innovation for the next phase of the region's major wins.

WINNERS

By 2022, Otsuka will lead growth with portfolio of psychiatry drugs

Eisai will add **$1.54bn** to the top line



Astellas is expected to launch **8 new products**

LOSERS

-$802m
Daiichi Sankyo losses from patent expiries

-1.2% CAGR
Kyowa Hakko Kirin revenues weighed down by heavy exposure to generics.

-600 jobs
Astellas reorganizes with competition for Micardis and Vesicare looming

THERAPEUTIC GROWTH BY 2027

Oncology will be a **$17bn** market

32% of US sales will come from oncology

CNS will be a **$14bn** market

25% will come from CNS

M&A

$16bn
revenues by 2027

A merger between Eisai and Otsuka would have multiple benefits and fast-track their mutual growth.

Source for all data: Datamonitor Healthcare's Pharmavitae

Novartis Pharma CEO On Star Products, Pricing And Rebates

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Paul Hudson, CEO of Novartis Pharma AG, discusses pricing, and expectations and dynamics around the company's star products including how Cosentyx (secukinumab) is sitting pretty in the rheumatology and psoriasis space, despite competition. Heart failure drug Entresto (sacubitril/valsartan), which is well on its way internationally, could potentially emerge as one of the most successful medicines ever launched by Novartis in India.

In an exclusive interview with *Scrip* at Novartis India's sprawling office in Hyderabad, Hudson also indicated that while there is a global "lack of understanding" of pricing of "cures" like gene therapies, the outlook of payers towards such products has been encouraging.

The Swiss multinational also appears to be keeping a close eye on potential opportunities around India's massive National Health Protection Scheme, expected to be rolled out next month. Dubbed "Modicare", akin to Obamacare in the US, the government-sponsored insurance aims to cover around 40% of India's population.

ANJU GHANGURDE: *It's probably tough times to be a CEO of pharma, what with escalating pricing pressures across key markets – the US, Japan and the goings on in China. What's your take on the ongoing action and how is Novartis balancing value and volumes given that science is currently probably at its exciting best with immunotherapies, gene therapy etc?*

PAUL HUDSON: It's a great time to be a pharma CEO, not least the underlying performance of our business is healthy and strong. We are growing volumes significantly – meaning we are helping treat unmet need. There is of course, never more so a desire for us to show the value that we bring to health systems across the world. People don't often mention Europe but we've been living with price controls and cost-effectiveness in Europe for two decades and we are one of the most successful organizations there. We have developed strong competency for demonstrating our value to payers and patients and health systems.

Clearly changing times in the US for sure. We worked tirelessly to be leaders of outcomes-based contracting – does our medicine do what we say it will do. We worked very hard to make sure we price responsibly. Our group CEO Vas Narasimhan reconfirmed that we won't take any price rise for the remainder of the year. That's more to guide for stability. Whilst we will maintain prices as they are, the pharmacy benefit managers [PBMs] will continue to ask for increasing rebates but that's the nature of where we live. We launched *Aimovig* (erenumab) very recently in the US and launched it below the cost effectiveness standard. And we did that because we realized the sheer scale of the unmet need. We didn't want patient/the health system affordability to affect this.

Wherever you go in the world innovation is still rewarded; innovation still has its place. And fundamental to any pricing discussion, I have to ask myself are we doing something better than standard of care – are we treating a disease that's an unmet need ; are we bringing value in a sustainable way to health systems? And I'm proud of the decisions from innovation to pricing that the company has taken. In Japan, we are putting our gene therapy [AVXS-101] through the approval process. The PMDA has awarded it a "Sakigake" designation -breakthrough. There's still a great desire for innovation to be rewarded. In China, the change in the rules where major medicines are going to be approved in China without additional studies because of the huge unmet need, and we are positioned well we think in the Chinese market, growing significantly. The quality of our medicines and indeed the quality of our generic medicines means that we have less exposure than many of the competition in terms of the new standards that the China government has set. In the US, the new administration is looking for opportunities to influence or change the pricing environment; they are not all list price some are Part B or Part D changes or suggested changes. We believe we have less exposure than other organizations in those environments.

AG: *But, in general is the pricing debate a bit too skewed against pharma in the US?*

PH: Like many things, if you only talk price, then you don't fully understand value. Whatever the price be, if it's only the sticker you are talking about then we would strongly encourage people to fully appreciate the value that we bring to patients, society and health systems. That said, we welcome further transparency on the role of the PBM, the role of the wholesaler and specialty pharmacy. Net rebates in the US are close to 40% for the industry. That's a big premium that's being passed on in the middle between the innovator and the patient for managing a formulary and for distributing medicines. I don't underestimate they play an important role but the transparency on the scale of that rebate is overdue. Before President Trump came in to begin his term, he raised many questions and I think since then the debate has opened up much more for people to understand who are all the players and frankly it's not just pharma in that equation.

AG: *Cosentyx had a great Q2 with sales of $701m and total number of prescriptions (TRx) in the US up by over 80%. (Also see "Cosentyx Carries Novartis Sales But Kymriah Manufacturing Gives Cause For Concern" - Scrip, 18 Jul, 2018.) Do you expect emerging competition from the IL-23 class to slow things down a bit – J&J's Tremfya (guselkumab) has a head-to-head trial with Cosentyx – or is Consentyx on course to take over from Humira?*

PH: Cosentyx's $701m in Q2 was a real statement of our ability to execute globally, not just the US. Here in India, our aspiration is to be the number one monoclonal antibody in the branded market for these patients over time. So, it's a worldwide performance, and a worldwide expectation. We tend to focus a little bit on the US because there is a net price debate –

what do you have to rebate for a position in a competitive market. We chose in Q1 to offer some additional rebate to make sure that we had the opportunity to be used in biologic-naïve patients. In the US, the IL-17 class is more effective in psoriasis than anti-TNF. But when *Humira* (adalimumab) is the anti-TNF, the rebating position means that you are used after Humira. Whilst that's ok, when you have aspirations to be a $4-5bn medicine, and frankly you just expect patients do better on Cosentyx than they do on anti-TNF, it's important to make sure you have access in earlier line. So we rebated, to make sure that we did not have to step through the competition. Where that led us is frankly we are a market leader on new patients in psoriasis - we are ahead of all of the new launch competition and we are also the market leader in rheumatology. Perhaps, what is not as well understood is that the patient population in rheumatology is as large as the patient population in psoriasis.

IL-23s - that's really competition in psoriasis; it is not competition in rheumatology because *Stelara* (ustekinumab), and now the IL-23s are showing themselves to be not as effective in rheumatology indications. You will have seen risankizumab decided not to pursue studies in ankylosing spondylitis for example. So, we know that in rheumatology there are only two players – us and there's **Eli Lilly & Co.** with *Taltz* (ixekizumab). We've seen in clinical practice we are able to preserve a sustained response for multi-years. We think we are unique. In psoriasis, we are the only medicine with five-year data. For similar reasons and that 90% of patients can retreat and capture response with Cosentyx, which is significantly higher than any of the competition because we are fully human [monoclonal antibody]. So, we think we are well differentiated in rheumatology, well differentiated in psoriasis but we accept psoriasis is more competitive. We've reconfirmed our commitment to consensus this year globally and so we'll be a multi-mega blockbuster by the end of this year.

AG: *Both Cosentyx and Entresto are available in India – how have they fared and are TRx growth levels significant? What about the prospects of using real world data from these products in India/China? (Also see "Real World Data Helping To Drive Rise Of Novartis' Entresto" - Scrip, 29 May, 2018.)*

PH: We guided at the half year, there is a good chance Entresto will be a blockbuster this year, which is a significant step in what was a slow launch. We learnt a lot from that launch which will help us longer term. The growth of Entresto now means that we are well on our way and we will be margin-accretive from the first day of 2019 and that is fantastic given the length of patent and the lack of competition – that's going to be a very important contributor to our success. What we are seeing in the real world is that the real world effectiveness of Entresto is being demonstrated as perhaps even stronger than we saw in the clinical work, which of course is designed mainly for approval. The symptom benefit is so significant that we know that patients are feeling different and able to do more.

A study in the US that's just been published shows that for a major US healthcare system if you use Entresto, you reduce the cost of treating a heart failure patient by almost 30%. That's total cost – so you add in Entresto and total cost goes down 30% including drug. That's where we should be because it allows health systems to be sustainable and patients to get innovation. Entresto is perhaps one of the best-ever launches in cardiovascular in India in recent history. Not only that, it's possible Entresto could go on to be one of the most successful medicines that our Indian organization has ever launched. And that just shows you the early physician and patient feedback in India. I had the opportunity to meet cardiologists from Hyderabad who reconfirmed to me that we need to partner on helping remote patients; we need to partner on demonstrating our value and providing services and education but they were very optimistic about the future of Entresto (sold as Vymada in India). So, overall the future of Entresto looks incredibly bright. The growth of Entresto and Cosentyx in our organization since 2015 has now given us a chance to demonstrate we know how to launch medicines.And with 11 launches over the next three years, that's very important.

MILAN PALEJA, COUNTRY PRESIDENT AND COUNTRY HEAD (PHARMACEUTICALS) NOVARTIS INDIA: Entresto India growth numbers are almost in line with global growth numbers and the number of heart failure patients in the country are so huge that we see, in the 'outer years', maybe our growth could be even faster. We have a co-marketing arrangement with **Lupin Ltd.** and **Cipla Ltd.** for the product.

AG: *Novartis hasn't really shied away from bringing in its latest products to India, but would pricing dynamics mean that products like Luxturna (voretigene neparvovec) – Spark launched the product at the list price of $425,000 per eye, or $850,000 for most patients in the US - or Aimovig aren't likely to be India-bound anytime soon?*

PH: In the US we, priced Aimovig with our partner *Amgen*, lower than cost effectiveness, meaning we are outperforming the contribution back to society and we've seen that reflected in the uptake. We will launch Aimovig in India in Q1 2020 and we haven't reached the decision on pricing but we know that the market in terms of value is very small. But we think that's because of a lack of understanding. So, as the market leader currently, it will be our responsibility to work locally to decide how to price and demonstrate value, depending on unmet need and opportunity. Importantly for places like India, price is sometimes just slightly less important than affordability. There is no point seeking a great price and then patients are unable to, from an out of pocket perspective, get access to the medicine. Most of the two days I've spent here has been how do you help somebody make a choice between a medicine, which we think has a low price, and perhaps cell phone data and other things that they would spend their money on.

For *Luxturna* and gene therapies there is global lack of understanding of what cures should be priced at. Gene therapies, particularly for monogenic diseases, is going to be a new science for many payers and regulators alike. We didn't price Luxturna in the US, when we are ready we will have those – we've started those conversations in Europe with reimbursement authorities. For Luxturna and indeed even more so for AVXS-101, our gene therapy in spinal muscle atrophy (SMA), payers have been very open to conversations. What you may think is a high price, they do recognize the investment needed to get the science to become a reality. And they also do recognize it's a very small number of patients. So, if you look at SMA

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there are about 700 babies born worldwide a year that suffer from SMA Type 1. 90% of those babies will die before their second birthday, so if you can cure them what does that mean. And payers are, we found, very collaborative in trying to find ways to appropriately bring those to market. For emerging markets, there is another level of complexity because there is often a basic level of healthcare investment required before scientific breakthrough and innovation.

AG: *How is Novartis looking at the ambitious Modicare plan - India's massive National Health Protection Scheme (NHPS), which expects to cover 100 million poor and vulnerable families with health cover for secondary and tertiary care hospitalization? What kind of potential partnership opportunities could it open up?*

PH: Any policy that tries to get access for patients that have no access and no coverage is to be applauded. It is a hard thing to execute universal insurance. Even in markets like the US we've seen that has been difficult to do. With the people that I've met, I feel that we need to and we are offering ourselves as a partner in that provision of health. It is one thing providing access but there is a great deal of education and person to person conversation that will be needed across the country. We talked to cardiologists about running heart failure clinics in 600 villages in remoter parts of this region. And they tell you how difficult it is even for out-of-pocket and even for patients who understand but can't get to see the right physician or need to be convinced to take a medicine. We think Modicare is a commitment to those most vulnerable probably, but the industry as a whole is going to have to work in partnership to try and make sure that volume is accessed appropriately. And where patients are still suffering, they get access to more innovative medicines after that.

MP: If you look at the current announcement of Modicare, it does not cover NCDs [non-communicable diseases] and outpatient expenses, and if you look at some of the current biggest health issues in the country, it includes NCDs. What would be important for us as a company and an industry is to work with the government to see how they can expand the coverage and further it is opened to even innovative medicines, which can be very helpful and where we are very keen to partner.

AG: *Novartis' stated long-term strategy is to emerge as a leading medicines company powered by data and digital. Do you see a significantly expanded role for India in the data and digital part going forward, given the IT prowess here and also India's ambition to be the "AI Garage for 40% of the world"? (Also see "India's Big AI 'Garage' Ambition – Can It Get The Mechanics Running ?" - Scrip, 25 Jun, 2018.)*

PH: It's not one garage. Remember we have the largest number of patients in a longitudinal data set out of any other pharma company or healthcare institution; we have close to two million patients' data that we can analyse for trends, themes, signals, drug hunting opportunities and there are different centers of excellence to do that type of work and different companies, who are growing from start-ups to become serious businesses to analyse that data in India and globally. When we get to the big data analytics and managing, on a worldwide scale, then it's most likely here in Hyderabad. Hyderabad has become a worldwide center of excellence for data, for digital, for analysis. It's pretty extraordinary. I don't think any other company has made the commitment we've made here in India. I go to other parts of the world and they talk with pride about how they are being supported from Hyderabad. That's quite an interesting sort of 'export' that comes from here that shouldn't be missed.

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received Takhzyro experienced 83% fewer moderate-to-severe attacks and 87% fewer attacks that needed on-demand treatment. After reaching steady state with therapy, 77% were attack-free at the end of six months.

Labeling recommends a 300 mg dose every two weeks, but says for some patients, monthly dosing can be considered after steady state is reached. By contrast, while Haegarda showed similar efficacy in a Phase III study (median reductions in monthly attacks ranging from 89%-95% compared to placebo), it is dosed at a much higher volume than Takhzyro, 60 iU/kg based on the patient's weight.

Jefferies' Steinberg pointed out that Takhzyro's dose is much lower in volume, with less frequent dosing than the CSL Behring product. "Haegarda's twice-weekly injections are arguably far less convenient than either the expected once-monthly or twice-monthly Takhzyro dosing," the analyst said. Also bullish on the product is BTIG analyst Timothy Chiang, whose Aug. 24 note on the approval predicts peak sales of $1.4bn-$1.5bn within five years of launch. Further, Chiang expects Takhzyro to catalyze continued growth for Shire's larger immunology portfolio.

"We believe the upcoming launch of Takhzyro could provide more visibility for the company's immunology segment, which we estimate will generate around $4.75bn in 2018 and around $5.04bn in 2019," he said. "We think the approval of lanadelumab will strengthen Shire's leading position in the HAE treatment market, with the potential for additional sales gains over the next two to three years."

Dosing convenience with Takhzyro also could net Shire a great number of patients than currently receive prophylactic therapy, Chiang said. Current estimates have 3,000-4,000 US HAE patients on prophylaxis. Takhzyro's efficacy and safety profiles and dosing convenience could double that number, the analyst predicted. While Takhzyro may cannibalize Shire's existing HAE portfolio, Jefferies' Steinberg noted, he thinks the new product will produce significantly higher sales margins than Cinryze or Firazyr. As a franchise, he anticipates the Takhzyro/Cinryze prophylaxis business will eventually top $2bn in annual worldwide sales.

The portfolio of four HAE therapies also could benefit Shire in terms of US market access, the analyst said, because it could position products with different price points and modalities "that could cater to different segments of the market."

Shire's Mayer told *Scrip* he thinks Phase III data showing that patients were able to self-administer Takhzyro in less than one minute might be its greatest selling point. "I think that creates a significant advantage compared to what is already out there," he said.

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GBT Picks Up Inclacumab From Roche's Bargain Bin

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Roche has become the latest pharmaceutical major this week, after **Gilead Sciences Inc.**, to unload what was once seen as a promising asset, handing inclacumab over to **Global Blood Therapeutics Inc.** for just $2m upfront.

The Swiss major has licensed inclacumab, a monoclonal antibody against P-selectin, to GBT, which plans to develop it for vaso-occlusive crises (VOC) in patients with sickle cell disease (SCD). Roche was previously evaluating the drug as a treatment for coronary artery disease but its silence on the compound has been deafening for over five years.

Sickle cell disease is an area of high unmet need

In March 2013, Roche presented data at the American College of Cardiology meeting which showed that inclacumab, which came out of a collaboration with **Genmab AS**, reduced heart tissue damage in patients with acute coronary syndromes who were dosed with the P-selectin antagonist prior to angioplasty in a Phase II trial. At the time, the study's lead investigator Jean-Claude Tardif from the University of Montreal, stated that the clinical benefit after a single injection of the antibody was "exciting," but needed to be replicated in larger studies.

Given the lack of news concerning inclacumab after that ACC meeting, it appears that Roche was not prepared to conduct those larger trials in a compound that Tardiff had claimed "could become part of the therapeutic armamentarium in modern cardiology." For whatever reason, Roche discontinued the inclacumab program following the aforementioned Phase II trials and now GBT has got hold it for a token upfront, although Roche is eligible to receive up to $125m in development and commercialization milestone payments for the sickle cell disease indication, plus tiered royalties.

GBT noted that "the pharmacokinetic, safety and tolerability profile of inclacumab are well characterized based upon Roche's prior clinical studies, which enrolled more than 500 patients." It added that P-selectin inhibition "is a clinically validated target in SCD, known to reduce the incidence of VOCs," and it has already begun the process of technology transfer from Roche to a contract manufacturing organization.

SHIFT TO SICKLE CELL DISEASE

Approximately half of individuals with SCD, a lifelong inherited blood disorder caused by a genetic mutation in the beta-chain of hemoglobin, experience VOC. The pain can affect any body part but often involves the abdomen, bones, joints and soft tissue, causing a decrease in quality of life and an increase in the risk of death.

The deal makes sense for GBT given that voxelotor, its lead investigational drug which is an oral, once-daily therapy, is in Phase III trials for SCD. CEO Ted Love said in a statement that the firm had been "working diligently to diversify our product pipeline through both internal research and external business development efforts" to become "the preeminent SCD company," and inclacumab was "an ideal complement to voxelotor."

In June, GTB noted that having held talks with the FDA, it was pursuing accelerated approval for voxelotor based on positive top-line data from part A from the Phase III HOPE study. On the primary endpoint, 58% of patients on voxelotor dosed with 1500 mg at week 12 achieved a greater than 1 g/dL increase in hemoglobin versus 9% on placebo.

Mark Breidenbach, an analyst at Oppenheimer, issued a note saying that inclacumab "could help fill a clinical benefit gap for patients receiving voxelotor," adding that available data suggest the latter "rapidly and sustainably reduces hemolytic anemia but may require extended dosing before a tangible VOC benefit develops. Inclacumab could provide an immediate VOC benefit," he added, writing that he sees the drug as "a complementary and logical addition" to GBT's pipeline.

SCD is an area of high unmet need. The generic chemotherapeutic hydroxurea has been the main approved treatment, but is associated with some severe toxicities that make it hard to use. **Emmaus Life Sciences Inc.**'s *Endari* (L-glutamine oral powder) got FDA approval last year as the first new drug approved for the disease in the US in almost 20 years. *(Also see "Emmaus Plans Modest Pricing In 4Q Rollout Of Sickle Cell Drug Endari" - Scrip, 9 Jul, 2017.)*

As for inclacumab, it will not be getting to the market any time soon as GBT said it did not anticipate submitting an investigational New Drug Application to the FDA until 2021. Potentially much closer to approval is **Novartis AG**'s crizanlizumab, which is also a P-selectin targeted antibody obtained through the November 2016 acquisition of Selexys Pharmaceuticals Corp, and is scheduled to be filed in the US by the end of 2018.

Roche's decision to divest inclacumab came a day after Gilead handed over the stalled Phase III Janus kinase 1/2 and activin receptor type 1 inhibitor momelotinib to **Sierra Oncology Inc.** for just $3m upfront. *(Also see "Sierra Believes It Can Do Better Than Gilead With JAK Inhibitor Momelotinib" - Scrip, 23 Aug, 2018.)*

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Future Looks Bright For Ambitious Argenx

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With **AbbVie Inc.** licensing a preclinical immuno-oncology drug, and strong data backing its lead candidate efgartigimod, **argenx SE** of Belgium's antibody technology platform has been validated.

The AbbVie deal, announced Aug. 22, saw the US major has exercised an option it took out in April 2016 to develop and commercialize ARGX-115, an antibody targeting glycoprotein A repetitions predominant (GARP) which plays a key role in the regulation of production and release of active transforming growth factor beta.

ARGX-115 is believed to selectively limit the immunosuppressive activity of activated regulatory T-cells (Tregs), thereby stimulating the immune system to attack cancer cells. The premise is that ARGX-115 could prove useful as monotherapy or in combination with anti-PD1/L1 and/or anti-CTLA4 agents, or with cancer vaccines, to improve the activity and safety of those immunotherapies.

An argenx spokesperson told *Scrip* that in the two years since AbbVie took out the option, a lot of preclinical work had been done and the partners hoped to enrol the first patient in clinical trials next year. The company banked $40m when the deal was announced and received $20m more. It is eligible to receive milestone payments of up to $625m, as well as tiered royalties, if all goes well in the clinic.

Argenx, which has bases in Ghent, Belgium and Breda in the Netherlands, has also secured co-promotion rights for ARGX-115-based products in the EU and Switzerland. AbbVie seems convinced of the candidate's potential and Tom Hudson, its head of oncology early discovery and development, noted in a statement that "our collaboration with argenx over the past two years has been productive and we look forward to continue working together to fuel scientific progress."

CEO Tim Van Hauwermeiren said the deal highlighted the important of argenx's Innovative Access Program (IAP) as ARGX-115 is the result of research initially carried out by the de Duve Institute/ Université Catholique de Louvain in Belgium. He added that the IAP "remains a strategic priority for us [and] we continue to seek out cutting-edge research and targets while advancing our current collaborations, all with the potential to broaden our pipeline and demonstrate our discipline as a strategic partner."

> "We continue to seek out cutting-edge research and targets while advancing our current collaborations, all with the potential to broaden our pipeline and demonstrate our discipline as a strategic partner

Two additional IAP programs have started to bear fruit. One is ARGX-116, discovered in collaboration with disease biology experts from Staten Biotechnology, which specializes in the field of dyslipidemia and the other is a pact with Broteio Pharma of the Netherlands to develop therapies for severe autoimmune diseases.

The deal went down well with investors, as argenx shares went up 4.7%, while analysts at JMP Securities issued a note saying that the AbbVie collaboration "further supports our view that the company's technologies are differentiated and important in the development of novel biologics to address unmet medical needs."

While getting AbbVie fully onboard is a validation of argenx' Simple Antibody technology, which employs llama immunization, the more immediate focus is on efgartigimod. The latter is a first-in-class antibody fragment designed for the treatment of patients with severe autoimmune diseases and the company is developing the drug in three indications.

Primary results from a Phase II trial for efgartigimod in idiopathic thrombocytic purpura are expected next month, with a more detailed set of data set to be presented at the American Society of Hematology meeting in San Diego in December. The company already has positive Phase II results from the drug in another indication, myasthenia gravis, and a Phase III trial is being prepared with 150 patients expected to be enrolled; it is also being tested in mid-stage studies for pemphigus vulgaris.

The argenx spokesperson told *Scrip* that the firm was looking to take efgartigimod into Phase III on its own and sees it as a pipeline-in-a-product opportunity. Argenx is focusing on the drug in rare diseases but the potential in bigger indications such as lupus and multiple sclerosis could make for partnering possibilities.

As for the rest of the pipeline, ARGX-110 is in a Phase II study for cutaneous T-cell lymphoma and in a Phase I/II trial in acute myeloid leukemia and myelodysplastic syndrome. Argenx also has a collaboration with **Leo Pharma AS** signed in May 2015 for ARGX-112 for inflammatory skin disorders.

In addition to an upfront and other payments, argenx could pocket up to approximately €100m as well as royalties on net sales of any product from the deal with the Danish company – a third preclinical milestone was banked in April this year following the approval of the clinical trial application (CTA) filing for ARGX-112. It also received a payment from **Shire PLC** triggered by the latter exercising its option to in-license an antibody. No details about the indication specifically being pursued have been disclosed but argenx rather vaguely notes on its website that it might be a therapy to treat a rare disease such as Hunter syndrome or Fabry disease, or for a specialist condition such as ADHD or ulcerative colitis.

Cashwise, argenx is in good shape after raising approximately $100m through a Nasdaq listing in May 2017 – its shares are also traded on Euronext Brussels. As of June 30, cash and equivalents amounted to €338.9m and the spokesperson noted that the firm has enough money to fund operations for at least the next couple of years.

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Evotec's CEO Explains Logic Behind Drug Discovery Pact With Novo Nordisk

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Evotec AG hopes its just-inked strategic pact with **Novo Nordisk AS** will move steadily from its preclinical stages – based on IP held by the Danish group – to a long-term drug discovery and development alliance in which the duo jointly own the assets.

That's the view expressed to *Scrip* by the biotech's Austrian CEO, Werner Lanthaler.

Under the alliance announced Aug. 22, Novo Nordisk aims to use Evotec's technology to advance potential proprietary small-molecule candidates from preclinical development to regulatory filing quickly for treating co-morbidities associated with diabetes and obesity, such as diabetic kidney disease, non-alcoholic steatohepatitis (NASH) and cardiovascular diseases.

It will use Evotec's INDiGO platform, which integrates operations and accelerates early drug candidates into the clinic using strategies designed specifically for the molecule, therapeutic area and strategic needs.

In an interview with *Scrip,* Lanthaler said, "This reflects the fact that Novo Nordisk, which is world leading in insulin, world leading in antibodies, hasn't built a small molecule presence; they were looking for a strategic partner and after studying the landscape, chose Evotec to provide that small molecule platform. And, as is typical of Novo Nordisk, they are starting off on this quest with a very long-term view, an approach which is very attractive to us."

EVOTEC EXECUTE VS EVOTEC INNOVATE

The intellectual property for the partnership comes from Novo Nordisk. "They have generated a very interesting piece of chemistry for this alliance, and so this partnership falls into what we call 'Evotec Execute', as opposed to 'Evotec Innovate' where the IP comes from us.

The Evotec Innovate segment focuses on investing and developing Evotec proprietary assets while its Evotec Execute activities are built on partners' intellectual property and use the Austrian group's integrated drug discovery and development tools and in-house know-how.

Evotec AG

'Novo Nordisk will initially give us one or two projects to work on and if they are satisfied we would hope it would lead to a broader collaboration, in similar ways to our partnerships with Bayer and Celgene. I'd hope that Evotec and Novo Nordisk could at some point then build joint IP on which to work together'

Evotec is already working with French drug maker **Sanofi** to research new diabetes medicines, having launched its strategic alliance, TargetBCD, three years ago.

In late 2016, Evotec and **Celgene Corp.** entered into a strategic drug discovery and development collaboration to identify disease-modifying therapeutics for a broad range of neurodegenerative diseases, while in October 2012. Evotec and **Bayer AG** entered an ongoing partnership in the disease area of endometriosis. "I see this agreement with Novo Nordisk as a starting point," Lanthaler said. "Novo Nordisk will initially give us one or two projects to work on and if they are satisfied we would hope it would lead to a broader collaboration, in similar ways to our partnerships with Bayer and Celgene. I'd hope that Evotec and Novo Nordisk could at some point then build joint IP on which to work together."

He said Evotec's R&D arrangement with the Danish diabetes specialist is fundamentally different from its alliance with France-based Sanofi, and that the two collaborations would be ring-fenced and kept separate.

WORKING ON CELL THERAPY

"With Sanofi we're working predominantly on cell therapy using joint IP but based IP we generated, therefore that partnership is being conducted within our Innovate segment," the CEO said. "With our Novo Nordisk alliance, the IP is 100% owned by them, and so it falls under our Execute operations."

He added, "We will keep the two operations separate – that between us and Sanofi and us and Novo Nordisk – and ensure that there is no overlap between the two."

With the Sanofi operations, R&D activities will be using Evotec's sites in Germany as well as in Sanofi's locations in Toulouse, France while with the Novo Nordisk collaboration "we'll be doing the R&D in the Evotec labs in Oxford, UK and in Verona, Italy, to make sure there is no overlap or conflict between the two," he explained.

Lanthaler said that one of the key messages from Evotec's pact with Novo Nordisk was that the Danish group is "re-opening its portfolio of options and pursuing those again in small molecules, such as NASH and the obesity space which they are already pursuing with other therapeutic modalities. We will help them do this."

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Dravet Syndrome: Now With Two Approved Treatments

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Dravet syndrome begins in early childhood, but following FDA approval of *Diacomit* (stiripentol) from **Biocodex** two drugs have been cleared this year to treat the disease in the US and, with multiple other treatment options in the pipeline, one more could be approved in 2019.

Gentilly, France-based Biocodex announced on Aug. 23 that FDA approved Diacomit for seizures associated with Dravet syndrome in patients aged 2 and older when already being treated with clobazam. The agency's Aug. 20 decision follows the approval in June of **GW Pharmaceuticals PLC**'s *Epidiolex* (cannabidiol) – a marijuana plant-based medicine that will launch after scheduling by the US Drug Enforcement Administration – and precedes a new drug application (NDA) filing planned for **Zogenix Inc.**'s ZX008 in the fourth quarter of this year.

Dravet is also known as severe myoclonic epilepsy in infancy (SMEI), because of its early onset, severity and potential for ataxia and psychomotor retardation and affects about 2,000 to 8,000 patients in the US. Seizures begin in most cases during the first year of life, with a high frequency of status epilepticus that contributes to mortality among the young patients. Diacomit will be available to treat the disease in US pharmacies in January.

Diacomit, approved in the US as capsules and a powder for oral suspension, is not a new drug outside of the US; it's been approved in Europe since 2007 and in Canada and Japan since 2012. Biocodex described the possible mechanisms of action for the anticonvulsant's effects as being mediated through the GABA-A receptor with potential inhibition of cytochrome P450 activity, which increases blood levels of the benzodiazepine clobazam and its active metabolite.

The 65-year-old private French firm's drug was approved in the US based on two studies in Europe, STICLO France and STICLO Italy, in which the primary endpoint was the responder rate, defined as the percentage of patients with a greater than 50% decrease in the frequency of generalized clonic or tonic-clonic seizures in a 30-day period compared with a four-week baseline period.

The responder rate in STICLO France was 71% for patients treated with Diacomit versus 5% in the placebo group. The responder rate in STICLO Italy was 67% versus 9.1%, respectively.

The most common adverse reactions to Diacomit across the trials were somnolence (67%), decreased appetite (45%), agitation (27%), ataxia (27%), weight loss (27%), hypotonia (24%), nausea (15%), tremor (15%), dysarthria (12%) and insomnia (12%). One patient discontinued treatment after experiencing status epilepticus and another discontinued due to drowsiness, impaired balance and sialorrhea.

GW Pharma's cannabinoid receptor-targeting drug Epidiolex was approved on June 25 for the treatment of Dravet and the larger rare seizure disorder Lennox-Gastaut syndrome. In a Phase III study in 120 children and young adults with Dravet syndrome and drug-resistant seizures who were receiving standard-of-care epilepsy drugs, including clobazam and valproate, the number of convulsive seizures during a 14-week treatment period dropped from 12.4 to 5.9 for in the Epidiolex arm versus a dip from 14.9 to 14.1 in the placebo arm.

Zogenix will seek approval for its ZX008 (low-dose fenfluramine) in Dravet syndrome later this year based on the results of two Phase III studies, including Study 1504, which evaluated the drug versus placebo on top of stiripentol and other epilepsy medicines in 87 two- to 19-year-olds for 15 weeks. Results reported in July showed a 54.7% reduction in the number of monthly seizures for ZX008-treated patients versus those given a placebo. The median decline in monthly seizures was 62.7% for ZX008 and 1.2% for placebo.

Biomedtracker notes that the Danish firm **Lundbeck Inc.** drug *Onfi* (clobazam) was in Phase III development as an adjunctive therapy for Dravet, based on the March 2015 initiation of the placebo-controlled CLOVER I study. However, the sponsor withdrew the study in September 2015 due to recruitment challenges, according to clinicaltrials.gov, and Lundbeck no longer includes the program in its late-stage pipeline.

Onfi was approved for Lennox-Gastaut in 2011. It was Lundbeck's top-selling drug in the first half of 2018 with DKK1.76bn ($274.6m) in sales, but FDA recently approved the first generic version of Onfi, which is set to lose patent exclusivity in October.

EpyGenix Therapeutics says it has three drugs in clinical development for Dravet, including the Phase I drug EPX-100, an antihistamine with antiepileptic activity via the serotonin (5HT) signaling pathways. The company also has two serotonin (5HT) modulators in Phase II – EPX-200, an FDA-approved weight loss drug, and EPX-300, an FDA-approved antidepressant and insomnia drug.

The Paramus, N.J.-based company is entirely focused on rare genetic epilepsies and says all three of its candidates have been granted orphan drug designations in the US, though no studies are listed on clinicaltrials.gov.

PTC Therapeutics Inc. in South Plainfield, N.J., is recruiting patients for a Phase II clinical trial testing *Translarna* it initiated in 2016 to test its RNA-targeting drug in epilepsy patients with a nonsense mutation in CDKL5 or Dravet syndrome. **New York University School of Medicine** is the study sponsor and PTC is listed as a collaborator.

Xenon Pharmaceuticals Inc. presented interim Phase I safety results in May and intends to report final Phase I data from healthy volunteers in the second half of 2018 for XEN901, a Nav1.6 sodium channel inhibitor. Phase II studies are planned based on the final Phase I results in adult focal seizures and rare pediatric epilepsies.

Biscayne Neurotherapeutics Inc., **Opko Health Inc.** and **Ovid Therapeutics Inc.** each have preclinical programs in Dravet syndrome, according to Biomedtracker. Opko's OPK88001 is an oligonucleotide that's designed to increase production of the sodium channel protein SCN1A and it is expected to move into the clinic this year. Biscayne's BIS-001 inhibits acetylcholinesterase to increase GABA levels that activate anti-excitatory pathways; it's in Phase II for the treatment of focal seizures in adults.

Ovid's TAK-935 is the cholesterol 24-hydroxylase (CH24H) inhibitor TAK-935 (OV935) that's being developed in partnership with **Takeda Pharmaceutical Co. Ltd.** with a Phase Ib/IIa study under way in adults with developmental and epileptic encephalopathies.

The companies expanded their partnership to additional adult and pediatric rare epilepsies in July. Among three new Phase II studies expected to begin in the third quarter of this year is ELEKTRA, which will evaluate TAK-935 versus placebo in 125 patients with Dravet and Lennox-Gastaut syndromes.

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Allergan's Ulipristal Gets An FDA Rejection

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A US FDA complete response letter (CRL) for **Allergan PLC**'s ulipristal acetate in the treatment of abnormal uterine bleeding in women with uterine fibroids removes an overhang on the company's effort to sell its women's health unit, but it will also negatively impact any potential valuation of the business.

The company announced the receipt of a CRL in response to a new drug application (NDA) for ulipristal Aug. 21, which was not a surprising development but a disappointing one for Allergan nevertheless. The prospects of the drug reaching the US market were diminished after reports of serious liver injury and hepatic failure in women taking the product came to light in Europe, where the drug is marketed by **Gedeon Richter PLC** as *Esmya*.

Allergan pumped up investors on the commercial potential of Esmya in 2017, promoting it as one of "six stars" that would help see the company through a looming patent cliff for the dry eye blockbuster *Restasis* (cyclosporine).

More recently, Allergan announced plans to sell its women's health and infectious disease businesses as it braces for the impact of generics, but bids for the women's health business have been constrained by the uncertainty around Esmya, management recently reported.

Trouble for Esmya began brewing late last year after reports of liver injury surfaced in Europe. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee initiated a review, and the European Commission eventually adopted recommendations in June that include regular liver testing for women taking the medicine and restrictions on the drug's use to women ineligible for surgery to treat uterine fibroids. Gedeon reported dramatically lower sales of the drug in the first half of the year. The European review led FDA to push back the PDUFA date for Allergan's NDA for ulipristal earlier this year to August.

Allergan didn't specifically say FDA was concerned about liver toxicity, but said the agency requested additional information, citing safety concerns regarding Esmya post-marketing reports outside of the US. The company said it plans to meet with FDA to assess next steps. The NDA for ulipristal, a selective progesterone receptor modulator (SPRM), was based on the results of two Phase III trials in the US and four EU registration studies. Allergan markets ulipristal in Canada under the name Fibristal.

"Allergan continues to believe in the need for novel treatment options for women who are looking for a non-surgical treatment for uterine fibroids," the company said in a statement.

Those interventions could be on the horizon, but marketed by other drug makers. **AbbVie Inc.** and **Neurocrine Biosciences Inc.** are on track to file a supplemental NDA for the gonadotropin-releasing hormone (GnRH) receptor antagonist *Orilissa* (elagolix) in 2019, having already announced data from two positive Phase III trials. The companies announced more data Aug. 22 from a Phase III extension study that was in line with the results seen in the prior studies. Orilissa was approved by FDA in June for the treatment of pain associated with endometriosis.

Myovant Sciences Ltd. is developing a similar GnRH receptor antagonist, relugolix, which is in Phase III with data expected in 2019.

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Lynparza Blazes PARP Trail In China

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Following a priority review, **AstraZeneca PLC** and **Merck & Co. Inc.**'s *Lynparza* (olaparib) has received approval from the China National Drug Administration (CNDA), for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

The clearance makes Lynparza the first ever PARP inhibitor to be approved in the country, which has been taking steps over this year to accelerate the availability of novel cancer drugs through priority and fast-track reviews, in tandem with price cuts to improve affordability for patients.

Roche's ALK inhibitor *Alecensa* (alectinib) has also just been approved in China for ALK+ non-small cell lung cancer, while Lynparza for the additional indication of breast cancer is among a group of products recently granted a review under the regulatory authorities' expanding fast-track system.

The new approval in the group of initial indications was granted based on two pivotal studies – the Phase III international SOLO-2 trial in BRCA-mutated, relapsed ovarian cancer, and the Phase II Study 19 trial as a maintenance monotherapy in platinum-sensitive relapsed ovarian cancer.

The first of these showed improved progression-free survival of 19.1 months versus 5.5 months for placebo, while Study 19 showed an overall survival of 29.8 months for the drug versus 27.7 months for placebo.

China is increasingly accepting foreign clinical data to support approvals, particularly in high medical need areas.

The approval for Lynparza means the drug is now available in 61 countries for various indications; the product was first approved for ovarian cancer in the US and EU in December 2014.

It is estimated that 22,500 women in China die every year from ovarian cancer and there are over 52,000 new diagnoses recorded annually. Platinum-based chemotherapy has so far been the only treatment option in the country for women with platinum-sensitive recurrent ovarian cancer, and no new medicines for this patient population had been approved in the last decade.

Competition in China's nascent PARP sector is looming however, with potential class rivals moving ahead across various indications.

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From the editors of PharmAsia News.

Japan Approval Another Boost For Tagrisso in 1L NSCLC

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A new approval from Japan's Ministry of Health, Labour and Welfare moves **AstraZeneca PLC**'s *Tagrisso* (osimertinib) into the first-line setting in this potentially large market for the treatment of inoperable or recurrent EGFR mutation-positive non-small cell lung cancer (NSCLC), adding to the epidermal growth factor receptor tyrosine kinase inhibitor's class lead in this indication.

As elsewhere, the approval was based on results from the global Phase III FLAURA trial, which included Japanese patients, and it came after a priority review granted by the ministry this February given the medical need for new effective therapies in the first-line setting.

Tagrisso was first approved in Japan in March 2016, again following a priority review, as a first-in-class therapy for the treatment of patients with EGFR T790M mutation-positive inoperable or recurrent NSCLC resistant to existing first-line EGFR-inhibitors.

Dave Fredrickson, head of AZ's Oncology Business Unit, said the new clearance would help in "replacing older medicines… given the high prevalence of the EGFR mutation in Japan."

HIGHER MUTATION RATE

While only around 10-15% of NSCLC patients in the US and Europe have EGFRm NSCLC, this proportion rises to 30-40% in Asia, and the secondary EGFR T780M resistance mutation – against which osimertinib is also active – causes resistance to standard EGFR inhibitors in around two-thirds of these.

Such patients are particularly sensitive to treatment with EGFR-TKIs, which act to block the cell signalling pathways that drive tumor growth. In addition, about 25% of patients with EGFRm NSCLC also have brain metastases at diagnosis (increasing to approximately 40% within two years of diagnosis), which can reduce median survival to less than eight months, AstraZeneca noted.

Osimertinib has shown clinical activity against CNS metastases, which in addition to its improved tolerability compared with earlier generation EGFR inhibitors, is expected to help the drug's competitive and commercial position. First-quarter sales of Tagrisso were $338m globally, making it the UK-based company's top-selling oncology product. Among its potential EGFR-targeting global rivals in Japan, **Pfizer Inc.** filed for the local approval of dacomitinib in NSCLC this May. However, some analysts see a limited threat from the molecule given tolerability questions and comparative data from the FLAURA trial showing progression-free survival (PFS) advantages for osimertinib.

FLAURA assessed the efficacy and safety of 80mg orally once daily versus standard-of-care first-line EGFR TKIs (either erlotinib (*Tarceva*) 150mg orally once daily or gefitinib (*Iressa*) 250mg orally once daily) in previously-untreated patients with locally-advanced or metastatic EGFRm NSCLC.

The double-blind, randomised trial included 556 patients across 29 countries, and incorporated sites in Japan.

Osimertinib demonstrated superior PFS of 18.9 months compared with 10.2 months for the comparator arm, and this benefit was consistent across all subgroups including in patients with or without CNS metastases, an important consideration in lung cancer patients.

Tagrisso 40mg and 80mg once-daily oral tablets have now received approval in 39 markets, including the US and Europe, for first-line EGFRm advanced NSCLC, and more than 75 markets, including the US, Japan, China and Europe, for second-line use in patients with EGFR T790M mutation-positive advanced NSCLC.

The drug is also being developed in the adjuvant setting in the ADAURA trial and in locally-advanced unresectable NSCLC in the LAURA program, and in combination with other treatments.

AstraZeneca is planning to launch at least six new medicines in the oncology space between 2014 and 2020, and Tagrisso and its expanded use are seen as key growth drivers within this sector.

The company's PD-L-targeting antibody *Imfinzi* (durvalumab) was approved in Japan for maintenance use in locally advanced NSCLC in July.

Among the other new indications and revised uses newly approved by the MHLW was **Kyowa Hakko Kirin Co. Ltd.**'s anti-CCR4 antibody *Poteligeo* (mogamulizumab) for relapsed/refractory cutaneous T-cell lymphoma (CTCL), a rare form of non-Hodgkin's T-cell lymphoma. CCR4 is frequently expressed on leukemic cells. A requirement for pre-treatment diagnostic testing of CCR4 expression has now been removed, and dosage and administration changed.

The modifications are based on results from MAVORIC, the largest global Phase III randomized trial of systemic therapy in CTCL, in which identification of CCR4-positive cells before enrollment was not required. The 372-patient trial compared the therapy with vorinostat in patients failing at least one prior systemic treatment.

The dosing regimen – which is now approved in Japan – involved weekly intravenous administration of 1mg/kg for the first 28-day cycle, then on days one and 15 of subsequent cycles.

Poteligeo was first approved in Japan if relapsed/refractory CCR4-positive adult T-cell lymphoma in 2012, and subsequently for relapsed/refractory CCR4-positive peripheral T-cell lymphoma and cutaneous T-cell lymphoma, and chemotherapy-naive CCR4-positive adult T-cell leukemia/lymphoma.

The antibody was also approved in the US in August 2018 for adult relapsed/refractory mycosis fungoides of Sezary syndrome (the most common type of CTCL) after at least one prior systemic therapy, and is under review in the EU for CTCL.

LINZESS FOR CONSTIPATION

The other line extensions approved by the ministry included **Astellas Pharma Inc.**'s *Linzess* 0.25 mg tablets (linaclotide; licensed from **Ironwood Pharmaceuticals Inc.**) for the additional indication of chronic constipation, other than constipation associated with organic disorders (defined as that caused by anatomical/pathological changes or abnormalities in the visceral, organic, nervous, or other tissues, detectable by radiography and endoscopy).

The guanylate cyclase-C receptor agonist was first approved in Japan in December 2016 (launched in March 2017) as the first prescription treatment in the country for adults with irritable bowel syndrome with constipation (IBS-C).

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J&J Sees A Path Forward For Xarelto In Post-Hospital VTE Despite MARINER Failure

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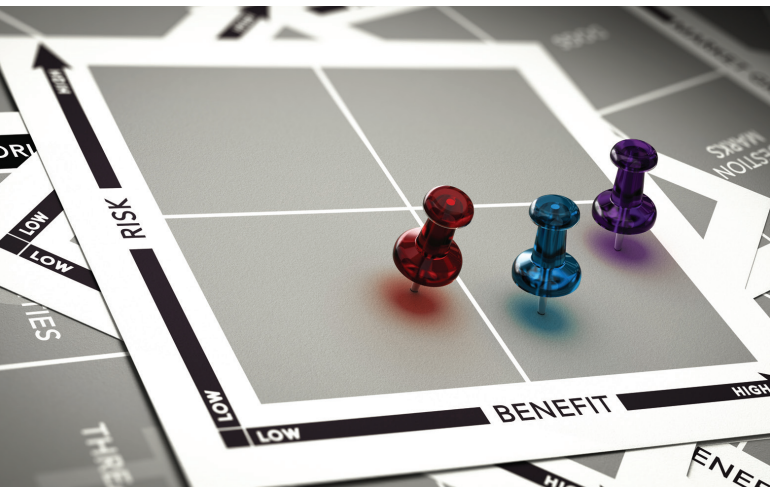

Johnson & Johnson's **Janssen Pharmaceutical Cos.** said on Aug. 27 that its oral anticoagulant *Xarelto* (rivaroxaban) is appropriate for the prevention of venous thromboembolic events (VTE) in certain acute medically ill patients following discharge from the hospital even though the Phase III MARINER trial in this population did not meet the primary efficacy endpoint.

Janssen believes that the MARINER data combined with results from the MAGELLAN study completed in 2011 show that Xarelto can reduce VTE in patients after they've been hospitalized for several days if administered to individuals who are not believed to be at high risk for bleeding events. The J&J subsidiary intends to discuss the cumulative data with the US FDA, but it will not pursue approval for the prevention of heart attack, stroke and death in heart failure patients based on results from the Phase III COMMANDER HF study.

MARINER and COMMANDER HF were presented at the European Society of Cardiology (ESC) meeting in Munich, Germany and published in the *New England Journal of Medicine* on Aug. 26 and 27.

"Combination of these [MARINER] results with those of the MAGELLAN trial tell a more complete story about rivaroxaban's role of preventing VTE in appropriately selected patients with acute medical illness," Janssen Research and Development LLC Global Therapeutic Area Head-Cardiovascular and Metabolism James List said during an Aug. 27 analyst call. "We see a filing pathway toward approval with these combined findings and look forward to discussing them with the FDA."

List said the effects of Xarelto on VTE was consistent across both studies, so results in this population from 20,000 patients enrolled in MARINER and MAGELLAN should be enough data for physicians to determine who can be appropriately treated with the drug following a lengthy hospital stay. He said the findings also should inform a discussion between Janssen and the FDA about a label allowing for the treatment of acute medically ill patients with a high VTE risk, but lower bleeding risk.

Xarelto is a Factor Xa inhibitor developed and commercialized under a partnership between Janssen and **Bayer AG**. Janssen markets the drug in the US, while Bayer sells it in the rest of the world.

Xarelto is indicated in the US for multiple VTE-related indications including for the prevention of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing knee or hip replacement surgeries; to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; for the treatment of DVT and PE; and to reduce the risk of recurrence of DVT and PE following six months of treatment for DVT and/or PE.

Janssen sponsored the MARINER and COMMANDER HF studies as part of Janssen and Bayer's EXPLORER program that includes several lengthy trials aimed at seeking additional indications for Xarelto or expanding the novel oral anticoagulant's label.

MARINER RESULTS MIXED, BUT INDICATE VTE BENEFIT

MARINER was a placebo-controlled pivotal study that enrolled 12,019 acute medically ill patients upon discharge from a three- to 10-day hospital stay for a variety of reasons, which may have included heart failure, infectious diseases, stroke, chronic obstructive pulmonary disease (COPD) or inflammatory diseases – a population with an increased risk of VTE for up to three months after leaving the hospital.

MARINER participants had to be at least 40 years old (mean was 69.7) with an assessed risk of VTE. They were treated from the time of hospital discharge for 45 days with Xarelto or placebo. Individuals receiving Xarelto were given a 10 mg once-daily dose if they had mild or normal renal function or 7.5 mg once daily if they had mild renal impairment.

The primary efficacy endpoint was the composite of VTE and VTE-related death, which occurred at a rate of 0.83% for Xarelto versus 1.1% for placebo – a 24% reduction, but that was not statistically significant (HR=0.76; 95% CI, 0.52-1.09; p=0.136).

List noted that "there was little difference between the study arms with respect to deaths adjudicated as related to VTE," but the rate of VTE alone for Xarelto versus placebo was significant at 0.18% versus 0.42% (HR=0.44; 95% CI, 0.22-0.89; p=0.023).

Indeed, Alex Spyropoulos of Lenox Hill Hospital in New York City and his co-authors wrote in the NEJM that "appropriate selection of medically ill patients may reduce the health burden of nonfatal venous thromboembolism in this population."

Despite the primary endpoint result, however, List also noted that when deaths from any cause, not just from VTE, were included in an exploratory secondary composite endpoint of symptomatic VTE and all-cause mortality the result was statistically significant at a rate of 1.3% for Xarelto versus 1.78% for placebo – a 27% reduction (HR=0.73; 95% CI, 0.54-0.97; p=0.033).

CONTINUED ON PAGE 18

SAFETY BETTER IN MARINER THAN IN MAGELLAN

The primary safety endpoint was major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria. Janssen said major bleeding was infrequent and the difference between Xarelto and placebo – 0.28% versus 0.15%, respectively (HR=1.88; 95% CI, 0.84-4.23; p=0.124) – was not significant. Non-major clinically relevant bleeding was higher with Xarelto at a rate of 1.42% versus 0.85% for placebo (HR=1.66; 95% CI, 1.17-2.35; p=0.004).

Bleeding "is a side effect associated with any anticoagulant medication, but the mixed results and failure to meet the primary endpoint may lead physicians to question whether the modest benefit of Xarelto use outweighs the potential deleterious effects seen with major bleeding and the statistically significant increase in risk of clinically relevant non-major bleeding," Biomedtracker said in an Aug. 27 report on the MARINER results.

Nevertheless, the Biomedtracker analysts noted that Janssen's "optimism regarding the possibility of indication expansion may not be misplaced," since **Portola Pharmaceuticals Inc.**'s newer Factor Xa inhibitor *Bevyxxa* (betrixaban) was approved in 2017 to prevent VTE in the same acute medically ill population even though the drug did not meet its primary endpoint with in the pivotal APEX trial.

"However, the APEX trial results were unique in that Bevyxxa failed to reach significance in a specific patient population (patients with an elevated D-dimer level), but did reach statistical significance within the larger at-risk population. This is not the case in the MARINER trial," Biomedtracker noted. "The APEX trial compared the use of Bevyxxa both within the hospital and after hospital discharge to the use of [**Sanofi**'s *Lovenox* (enoxaparin)]."

Treatment with Xarelto in MARINER did not begin until after patients were discharged from the hospital, but MAGELLAN did include treatment in the hospital and out of the hospital. That was one of a handful of changes from MAGELLAN that Janssen instituted in MARINER to improve safety findings, since MAGELLAN succeeded on efficacy, but had a bleeding rate that was deemed unacceptable. Other changes in MARINER included the lower 7.5 mg dose for patients with moderate renal impairment and exclusion of patients deemed to have a higher bleeding risk.

"Despite the mixed [MARINER] results, it is possible that Xarelto sees an approval for this indication without reaching its primary endpoint. However, even if the indication is approved, it is unclear how the mixed results of this study will impact the actual use and uptake since the VTE prophylaxis space is fairly new," Biomedtracker's analysts said.

DISAGREEMENT ON APPROVABILITY, IMPACT ON BEVYXXA

"Bevyxxa was the first novel oral anticoagulant (NOAC) approved for the indication and has experienced slow uptake," they continued. "It will be interesting to see if uptake of Bevyxxa is slow because of external issues such as unfamiliarity with the drug, reimbursement concerns and availability of the drug, or whether there is a lack of need within the indication itself. If the former is true, Xarelto may benefit from broad familiarity regardless of disappointing trial results."

It may be difficult to compare across the MARINER and MAGELLAN studies for Xarelto and the APEX trial for Bevyxxa, however, because Portola's study enrolled older patients who spent more days in the hospital than those in the Janssen trials, according to William Blair analyst Matt Phipps. Phipps did not see the MARINER results as guaranteeing an approval for Xarelto for the same indication that was approved for Bevyxxa, but he also does not expect the MARINER results to reduce the pressure on Portola in marketing its drug.

"Although we believe the removal of potential competition is a positive for Portola, we note significant work is still needed to gain adoption of Bevyxxa in the United States, and therefore the MARINER results do not significantly alter the near-term headwinds for Bevyxxa, in our view," he wrote in an Aug. 27 note to Portola investors.

HEART FAILURE STUDY IS A WASH

The result of COMMANDER HF, however, clearly showed that Xarelto did not make an impact in this indication. The study looked at whether Xarelto could reduce the risk of heart attack, stroke and death in 5,022 patients who experienced a recent episode of acute decompensated heart failure (ADHF) and had symptomatic heart failure for at least three months.

The primary efficacy endpoint was a composite of heart attack, stroke and all-cause death and the result was not significant with a 25% rate of those events for Xarelto plus the standard of care versus 26.2% for the standard of care alone, which was at the treating physicians' discretion, but could include aspirin or dual antiplatelet therapy (HR=0.94; 95% CI, 0.84-1.05; p=0.270).

There were numerically fewer heart attacks for Xarelto versus the standard of care, occurring at a rate of 3.9% versus 4.7%, respectively (HR=0.83; 95% CI, 0.63-1.08; p=0.165), and fewer strokes (2% versus 3%; HR=0.66; 95% CI, 0.47-0.95; p=0.023). However, Janssen noted that the lack of a difference in the rate of deaths, which comprised about 80% of the primary endpoint in both groups, suggested that the high death rate in these patients is driven by poor heart function rather than thrombotic events.

List noted that secondary endpoints in COMMANDER HF also did not show a benefit for Xarelto therapy in heart failure patients, including rehospitalizations.

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Pfizer Has Tafamidis Data In Hand, But Market Development Still A Challenge

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Phase III data showing tafamidis can reduce all-cause mortality and cardiovascular-related hospitalization has **Pfizer Inc.** anticipating a potential rare disease blockbuster, but it conceded Aug. 27 that first it will have to make substantial efforts to build the market in transthyretin cardiomyopathy (ATTR-CM).

Analysts swooned at the data showing a 30% reduction in all-cause mortality and 32% decrease in cardiovascular-related hospitalization at 30 months compared with placebo, projecting a future blockbuster for Pfizer in an indication with no current therapeutic option beyond heart or liver transplantation.

But first Pfizer will have to leverage the Phase III ATTR-ACT data, presented at the European Society on Cardiology Congress Aug. 27 in Munich, and push diagnosis, to establish a market for the cardiac form of transthyretin-mediated amyloidosis.

"Management noted that increasing awareness of the disease and diagnosis rates will require significant market development, and that the company is well positioned for this given its experience in cardiology," Deutsche Bank analyst Gregg Gilbert said in an Aug. 27 note. He predicts a US approval and launch in 2020 for tafamidis and peak sales of $1bn or greater.

A widely underdiagnosed or misdiagnosed form of heart failure, ATTR-CM affects an estimated 400,000-500,000 people in the US and Europe, according to Pfizer, but less than 1% of them likely are diagnosed presently. Between 15% and 25% of the worldwide disease population is thought to be in the US.

Diagnosis may improve, however, now that the old standard of biopsy can be replaced with the nuclear imaging test scintigraphy and the pharma also anticipates significant clinician enthusiasm for tafamidis, an oral, daily tablet, as it could offer the first therapeutic option for ATTR-CM beyond heart or liver transplantation.

To build a market in ATTR-CM, Pfizer must address several factors, execs told a same-day investor call.

"The disease is often initially misidentified as more common types of heart failure, but the symptoms persist and patients may consult with several cardiologists over time," said John Young, group president of Pfizer Innovative Health. "Unfortunately, once patients receive the accurate diagnosis of ATTR-CM, the median life expectancy in untreated patients is reported to be only 2.5 years in those with the hereditary form and 3.6 years for the those with the wild-type form. We have a large task in front of us: the first and foremost, help cardiologists to better understand this disease; and drive patients to centers of excellence."

Developing the market in ATTR-CM must start with increasing diagnosis of the disorder, Pfizer's Global President-Rare Disease Paul Levesque told the call. He estimates that there are about 50 centers of excellence in the US, and noted that availability of scintigraphy at these centers is more widespread than Pfizer anticipated.

"Improving diagnosis rates will rely on several factors, including expanding the number of centers of excellence and driving patients in those centers, use of scintigraphy," he said, adding that the lack of a drug therapy probably is among the reasons for the low diagnosis rate. "Pfizer will continue to remain active in educating cardiologists and collaborate with key stakeholders in organizations to support awareness, training, tools to accelerate and expand diagnosis ahead of the potential launch of tafamidis."

RESEARCHERS QUESTION TIMING OF THERAPY

The ATTR-ACT data confirm the optimism Pfizer previously hinted at in March, when top-line data for tafamidis suggested new promise for a drug that had been stalled since an FDA complete response letter in 2012.

Simultaneous with the ESC presentation, the ATTR-ACT data were published online in the *New England Journal of Medicine*.

"Given the dearth of acceptable treatments for this disorder, these robust efficacy results, combined with a benign safety profile, suggest an important role for tafamidis in the treatment of transthyretin amyloid cardiomyopathy," Cristina Quarta, University College London, and Scott Solomon, Brigham & Women's Hospital, said in an editorial on the study data.

The editorial notes that the study results do raise questions about tafamidis' mechanism of action, the time course of benefit and timing of treatment over a patient's course of disease. Quarta and Solomon note the drug – which binds to and stabilizes the structure of transthyretin – only showed reductions in hospitalization after nine months and a mortality benefit at 18 months.

"Moreover, a subgroup analysis showing greater benefit in patients with less severe heart failure suggests that treatment might best be initiated at an early stage of disease, when the underlying pathology may be more easily reversed as compared with later stages," the authors state. "It is possible that by slowing or halting amyloid deposition, tafamidis may allow the activation of local recovery processes that progressively result in a remodeling of the amyloid deposits, a reduction in the strain on the cardiac walls, and ultimately in a clinical benefit. Once amyloid has caused irreversible organ damage, disease-modifying treatments may be less likely to be effective."

SIZING UP THE COMPETITION

Earlier in August, RNA-interference pioneer **Alnylam Pharmaceuticals Inc.** obtained its first regulatory approval, getting a US FDA nod in hereditary transthyretin-mediated amyloidosis (hATTR) with *Onpattro* (patisiran), but the indication was narrower than the biotech had hoped and the label included no data on cardiovascular endpoints. ATTR-CM is a sub-indication of hATTR and Pfizer noted that its ATTR-ACT study was the first Phase III trial testing a drug therapy in ATTR-CM.

Besides Onpattro and tafamidis, the only other advanced drug candidate in this therapeutic area is **Ionis Pharma-**

ceuticals Inc.'s *Tegsedi* (inotersen), an antisense therapeutic awaiting FDA approval for hATTR, with a regulatory decision expected in October. That candidate also is in Phase II for ATTR-CM. Tegsedi obtained a recommendation for approval from the European Medicines Agency (EMA) in June, while tafamidis is approved in Europe under the brand name *Vyndaqel* for related indication of familial amyloid polyneuropathy (FAP).

However, there is additional activity earlier in the pipeline. Start-up **Eidos Therapeutics Inc.** is trying to ride the wave of amyloidosis drugs with its own small molecule for ATTR.

Young noted that tafamidis' two potential competitors have only been studied in polyneuropathy and have not been studied in wild-type patients. "I certainly don't want to speak for competitors and their data, but I think the likelihood is that … our data set will set a very high bar for others to be able to demonstrate their effectiveness in this [ATTR-CM] patient population," he told the call. The mortality and hospitalization benefits demonstrated In the 441-patient ATTR-ACT study go beyond efficacy levels many analysts have said would indicate significance, ISI Evercore analyst Umer Raffat said that a longer trial likely would have shown an even greater mortality benefit compared to placebo. On the investor call, Brenda Cooperstone, Pfizer's chief development officer for rare diseases, said an ongoing extension protocol may reveal a greater benefit long-term.

"It is certainly possible that with further follow-up, we will see further separation in terms of the mortality and therefore an increasing survival benefit, and we do have an ongoing open-label extension, which will give us further information with regard to the mortality in the longer term," she noted.

Pfizer reported that the trial showed a consistent directional mortality benefit across all patient subgroups. Secondary endpoints demonstrated a reduced decline in six-minute walk test distance and reduced decline in a quality of life assessment as well. Meanwhile, the drug showed an observed safety profile similar to placebo. The discontinuation rate in the study was higher in the placebo group than in either of the treatment arms, which tested daily 20 mg and 80 mg doses of the oral tablet, respectively.

BMO Capital Markets analyst Alex Arfaei said in an Aug. 27 note that as the diagnosis rate for ATTR-CM improves over time, Pfizer should gain a significant share of the market if tafamidis gets FDA approval. He predicted ex-US business will comprise about half of the drug's peak revenues, which he pegs at $1.3bn in 2027.

A key remaining question will be whether Pfizer seeks and/or obtains approval of tafamidis at the 20 mg or 80 mg dose. The ATTR-ACT study used a 2:1:2 randomization protocol, meaning that twice as many patients received the 80 mg dose as the 20 mg, and that the control group was the same size roughly as the 80 mg group. Approval of the larger dose in the US probably would mean a higher price – Levesque said the average annual price per patient in the EU and Japan for Vyndaqel is about $75,000.

The BMO blockbuster sales estimate for tafamidis is based partly on an expectation for US pricing of about $250,000, Arfaei said.

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Novartis' SOLAR-1 Shines on Alpelisib In Breast Cancer

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Novartis AG's PI3K inhibitor, alpelisib (BYL719), has met the primary endpoint in the global Phase III SOLAR-1 trial, showing an improvement in progression-free survival (PFS) in patients with PIK-3CA-mutated HR+/HER2- breast cancer.

The Basel, Switzerland-based multinational says the results will lead to the start of discussions on marketing submissions with regulatory authorities worldwide.

Adverse events observed in SOLAR-1 when alpelisib was combined with the marketed estrogen receptor modulator, fulvestrant, were generally consistent with those observed in previous studies with alpelisib and fulvestrant, the company said in its Aug. 23 announcement.

However, further details on the efficacy and tolerability of alpelisib were not given, with the company saying further results would be presented at a forthcoming medical conference. Of interest will be the candidate drug's effects on secondary endpoints such as overall survival, overall response rate, clinical benefit rate, efficacy in the PIK3CA non-mutated cohort, and safety and efficacy.

According to analysts at Datamonitor Healthcare, the development of PI3K inhibitors in this indication has been difficult due to limited efficacy and adverse events, and Novartis is hoping the alpha isoform-specific inhibition of alpelisib will lead to higher selectivity and a better tolerability profile than those reported with its pan-PI3K inhibitor buparlisib, which failed in the Phase III BELLE-3 trial.

OTHER COMPANIES

Roche's alpha-specific PI3K inhibitor taselisib also recently failed in the clinic, the analysts note. In the Phase III SANDPIPER trial, taselisib's two-month PFS improvement was statistically, but not clinically, significant, and the tolerability profile was again suboptimal and did not reflect an improvement over pan-PI3K inhibition. As such, the full SOLAR-1 dataset is needed to determine the potential of alpelisib in this indication.

Alpelisib has shown promise when used for PROS (PIK3CA-related overgrowth spectrum) in a group of French patients, and Novartis is exploring options to evaluate alpelisib in a clinical study, the company told *Scrip*. And buparlisib (BKM120), has just been out-licensed to the Hangzhou, China-based company, **Adlai Nortye**. Buparlisib has shown activity in combination with paclitaxel in patients with head and neck squamous cell carcinoma, and Adlai Nortye presented a thoughtful clinical plan for its future development, Novartis said.

Pfizer Inc. also has a dual inhibitor of PI3K and mTOR, gedatolisib in Phase I in solid tumors, and **Eli Lilly & Co.** is also studying a dual PI3K/mTOR inhibitor. In a brief reaction note to the SOLAR-1 data, Jefferies analysts estimated peak annual sales of alpelisib could reach $1.5bn annually. There are no approved PI3K inhibitors for HR+ advanced breast cancer.

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

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

Selected clinical trial developments for the week 17–23 August 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III INTERIM/TOP-LINE RESULTS			
Novartis AG	alpelisib	breast cancer	SOLAR-1; met primary endpoint.
Novo Nordisk	semaglutide, oral	type 2 diabetes and renal impairment	PIONEER 5; met primary endpoint, well tolerated.
MC2 Therapeutics A/S	MC2-01 (calcipotriene and betamethasone) cream	psoriasis	Superior to *Taclonex* topical suspension, well tolerated.
AstraZeneca	*Bevespi Aerosphere* (glycopyrronium/ formoterol)	chronic obstructive pulmonary disease	AERISTO; mixed effects, well tolerated.
AbbVie Inc.	*Orilissa* (elagolix)	uterine fibroids	ELARIS-UF EXTEND; reduced menstrual bleeding.
UPDATED PHASE III RESULTS			
Neurocrine Biosciences Inc.	*Ongentys* (opicapone)	Parkinson's disease	BIPARK I; reduced off-time.
Neurocrine Biosciences Inc.	*Ingrezza* (valbenazine)	tardive dyskinesia	KINECT 4; clinical improvements.
PHASE III INITIATED			
Bristol-Myers Squibb & Co.	BMS-986165	psoriasis	POETYK-PSO-1; in moderate to severe disease.
Impel Neuropharma Inc.	INP-104 (intranasal dihydroergotamine mesylate)	migraine	STOP-301; long-term intermittent use.
Can-Fite BioPharma Ltd.	piclidenosan	psoriasis	Comfort; in moderate to severe disease.
PHASE III ANNOUNCED			
Ono/Takeda	*Cabometyx/Cometriq* (cabozantinib) and nivolumab	renal cell cancer	CheckMate 9ER; in Japan.
PHASE II INTERIM/TOP-LINE RESULTS			
Kyowa Hakko Kirin Co. Ltd.	KW-6356	Parkinson's disease	Well tolerated and effective.
Vectura Group PLC	VR647 (budesonide) nebulizer	asthma in infant and pediatric patients	Reduced delivery time and ease of use shown.
Taiwan Liposome Co. Ltd.	TLC599	osteoarthritis pain	Met endpoints.
UPDATED PHASE II RESULTS			
Principia biopharma Inc.	PRN1008	pemphigus vulgaris	BELIEVE-PV; well tolerated, lowered auto-antibody levels.
Cellectar Biosciencies Inc.	CLR 131, radio- iodinated phospho-lipid drug conjugate	multiple myeloma	Signs of clinical benefit, well tolerated.
PHASE II INITIATED			
A C Immune, Ltd.	ACI-24, anti-Abeta vaccine	Alzheimer's disease	ACI-24-1801; in mild disease.
MediciNova Inc.	MN-166 (ibudilast)	alcohol use disorder	NIAAA RO1; in treatment-seeking patients.
Rexahn Pharmaceuticals, Inc.	supinoxin with pembrolizumab	breast cancer	In metastatic disease.
Sihuan Pharma Holdings Group Ltd.	KBP3571 (anaprazole)	duodenal ulcer	In China.

Source: Biomedtracker | Informa, 2018

MC2 Plots Course For Topical Psoriasis Drug Launch

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The private Danish company **MC2 Therapeutics** is preparing for the launch of its first drug, a topical cream MC2-01 (calcipotriene/betamethasone) for psoriasis based on its proprietary PAD technology, now that the drug has shown superiority in a Phase III trial over **Leo Pharma AS**'s *Taclonex*, a commonly used first-line therapy. MC2 said it will file a new drug application (NDA) with the US FDA for MC2-01 in the first half of 2019.

On Aug. 21, the company announced the positive Phase III data showing MC2-01 demonstrated superiority to Taclonex based on a decrease in the Physician Global Assessment (PGA score) of 40.1% versus 24% after eight weeks, and meeting the primary endpoint of non-inferiority of MC2-01 to Taclonex. The study met key secondary endpoints as well, including superiority to Taclonex on the percent reduction in mPASI score from baseline at Week 8 (64.8% versus 52.3%) and patient convenience. The trial enrolled 796 patients.

Launching a new drug in the highly competitive market for topicals for psoriasis won't be easy, as the category is also dominated by generics. But MC2 believes MC2-01 offers an important advantage when it comes to the convenient formulation.

"There are two things patients need. One is very effective relief of symptoms and fast, and they need a product that is doable for them, very convenient to use and absorbs quickly into the skin," President Jesper Lange told *Scrip*. "Traditional solutions have only focused on efficacy and fast onset, but they are Vaseline-like ointments, which are very good at driving molecules into the skin to target tissue, but they leave the skin very greasy and are not very good for putting on clothes."

A formulation that is easier to apply could improve compliance and thus efficacy. Some research has shown as many as 73% of patients on topical drugs for psoriasis do not comply with their treatment, according to the company.

MC2-01 represents the first time the vitamin D analogue calcipotriene has been combined with the steroid betamethasone in an aqueous solution, MC2 noted. Taclonex combines the same active ingredients in a topical suspension. Leo Pharma is an experienced dermatology player that generated DKK3.59bn ($600m) from psoriasis products in 2017. But the company reported that sales of Taclonex declined 24% in the US in 2017, with the topical psoriasis market dominated by generics. Leo Pharma has turned its marketing focus to *Enstilar*, a topical foam containing the same two active ingredients.

MC2 is a small company, just 16 employees, but would consider launching the product independently if it is approved by the FDA. It has not ruled out working with a larger commercialization partner either, Lange said. "The goal of MC2 Therapeutics is to build a new pharmaceutical company based on this [PAD] technology," Lange said. The company, which started in 2010, is studying other topical and ophthalmology formulations with the technology, including a formulation of cyclosporine, the active ingredient in **Allergan PLC**'s *Restasis*, in Phase II development for dry eye.

"We aren't ignorant to the cost involved in building a US sales force," Lange said. But he said the company's two investors, two Danish families, are aware of the potential investment and commercial opportunity.

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Executive	To Company	New Role	From Company	Previous Role	Effective Date
Laura Barrow	Achillion Pharmaceuticals Inc	Vice President, Clinical Operations and Head of Project Management	Synergy Pharmaceuticals	Lead, Program	21-Aug-18
Steven Zelenkofske	Achillion Pharmaceuticals Inc	Chief Medical Officer and Executive Vice President	UniQure	Chief Medical Officer	21-Aug-18
Kevin Green	AIVITA Biomedical	Vice President, Business Development	Allergan	Senior Director of Business Development	16-Aug-18
Scott Burell	AIVITA Biomedical	Chief Financial Officer	CombiMatrix Corporation	Chief Financial Officer	16-Aug-18
Iain Duncan	AVM Biotechnology	Chief Operating Officer			6-Aug-18
Patrick Lockwood-Taylor	Bayer Corporation	Regional President, Consumer Health, North America	The Oneida Group	Chief Executive officer	13-Aug-18
Michael T. Klimas	Indi Molecular	Senior Vice President of Strategy and Technical Business Development	Merck Research Laboratories	Executive Director Translational Biomarker Immuno-oncology and Cardiometabolic Lead	22-Aug-18

Source: Biomedtracker | Informa, 2018

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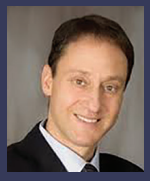

Professor Kenneth Getz, Director and Associate Professor at **CSDD**, **Tufts University School of Medicine**, *USA*

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