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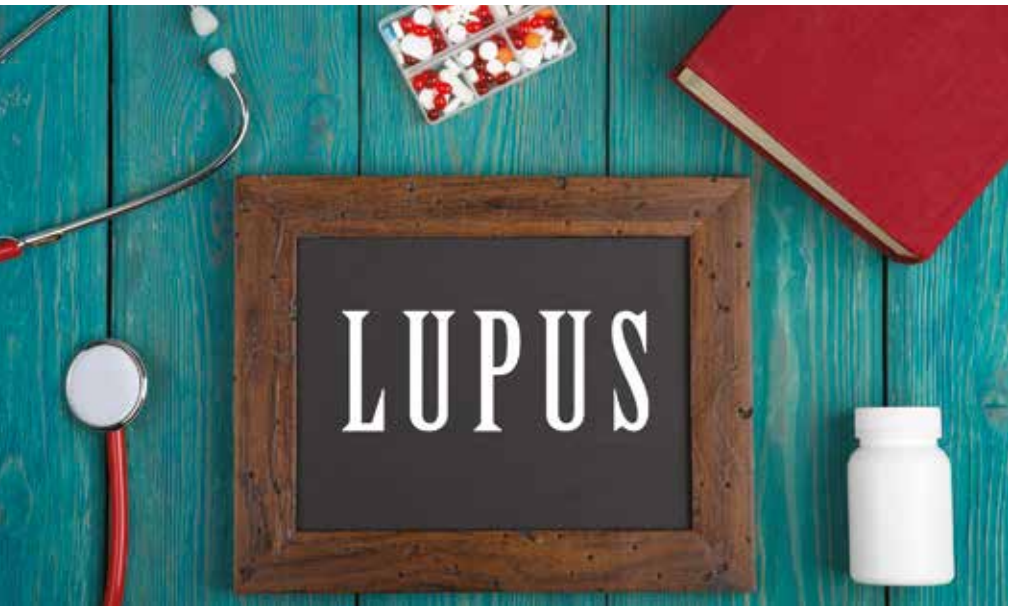

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Lupus Market Snapshot: It's A Blockbuster Opportunity

JESSICA MERRILL jessica.merrill@informa.com

Lupus is a category that has experienced lots of setbacks and disappointments, but the tide appears closer to turning than ever before given the large number of promising drugs for lupus advancing through the pipeline.

Scientific advancements and better understanding of the disease are helping to fuel the investment, but lupus also remains an autoimmune disease with few treatment options at a time when other autoimmune diseases like rheumatoid arthritis, psoriasis and ulcerative colitis have become ultra-competitive.

"I look at lupus as where we were with rheumatoid arthritis 15 or 20 years ago, and it was very new ground at the time. Now it is, for industry, one of the biggest categories that we have," **AstraZeneca PLC**'s global commercial head Brad Nohe told *Scrip*.

"I don't think lupus will reach the size of the RA market – it's a different patient population. However, lupus is a really substantial opportunity for us as industry, and for the community to bring new medicines to market that will address patient needs and the underlying pathophysiology of the disease," he said.

Industry experts working in the field are convinced lupus is a multibillion-dollar commercial opportunity, despite the fact the disease presents particular drug development and commercial challenges. Most notably, lupus is an incredibly heterogeneous disease, which manifests itself in many different ways that affect different parts of the body, sometimes the skin, sometimes the joints, and other times vital organs, like the kidneys.

Lupus already is segmented into different subtypes – the more common chronic systemic lupus erythematosus (SLE) that waxes and wanes, the acute condition lupus nephritis that affects the kidneys and can lead to kidney failure, and cutaneous lupus erythematosus, which affects the skin – but many expect the space will become even more segmented as knowledge grows. At the heart of the disease is a hyperactive immune system that attacks the healthy cells in the body.

"All of the drugs that are going to be developed for lupus are going to serve one subset of the population," Lupus Foundation of America CEO Sandra Raymond said. "I don't think we are going to see a drug, although we may, by 2020 or 2021 that is going to be a breakthrough drug for everyone who has lupus."

LEARNING FROM BENLYSTA

The result is that despite industry's apparent confidence, it remains unclear how many lupus patients would be candidates for what would likely be a premium-priced biologic drug. There are even now discrepancies about the prevalence of the disease among the different stakeholders working in the area.

GlaxoSmithKline PLC's *Benlysta* (belimumab) remains a shadow that hangs over the therapy area when it comes to the commercial realm. The first-in-class BLyS-specific inhibitor, developed with partner **Human Genome Sciences Inc.**, launched with a lot of fanfare in 2011 as the first new drug for

CONTINUED ON PAGE 9

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

from the executive editor

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R&D and deal-making are the lifeblood of the pharmaceutical and biotech industries and the quiet weeks of August have given us a little more time to take a deeper look at these key areas.

A new report form Trialtrove shows the extent to which cancer is taking over clinical research. The findings looking at clinical trial starts in 2016 show that the number of studies of anticancer products was more than three times the number of the next most popular area, CNS.

The research also breaks down the studies into those of totally novel drugs and those testing already approved products to give us some idea of the extent to which label expansions are being sought in the different therapy areas.

The results make for interesting reading – while oncology having a high proportion of new studies of marketed drugs is to be expected given the pursuit of multiple indications for the immuno-oncology products, it is perhaps more surprising the CNS had similar proportion of trials of already approved drugs starting last year. And it looks like most innovation is taking place in ophthalmology. See story on p12-14 for more details.

Meanwhile, a close examination of licensing trends in the CNS area from Datamonitor Healthcare shows that while there were fewer deals last year involving drugs for central nervous system disorders those that were inked were worth more. In 2016, the potential deal value for CNS therapies rose to more than $12bn – Lucie Ellis has more details on p16-17.

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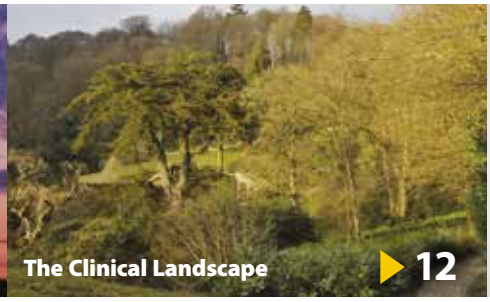

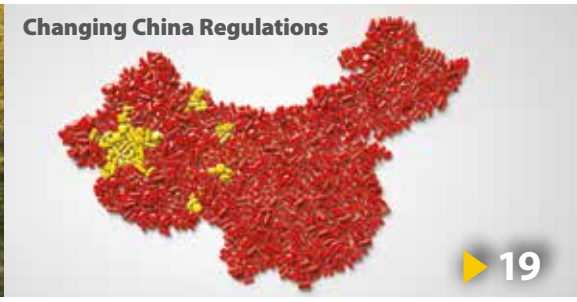

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A product derived from a bacterial protein, IdeS, could be the first medicine from Sweden's Hansa Medical to tackle a serious unmet need, transplant patients unable to find a donor match because of HLA sensitization.

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Mallinckrodt's InfaCare Buy Leaves Room For Further Diversifying M&A
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UK-based Mallinckrodt's purchase of InfaCare gives it a late-stage asset for severe jaundice in infants while leaving room for further M&A.

Zynerba's Cannabidiol Failure in Focal Seizures Not So Clear-Cut
http://bit.ly/2vwKnqZ
Zynerba's gel formulation of cannabidiol has disappointed in top-line data from a Phase II study in epilepsy patients with focal seizures, but some signals of efficacy in a companion study, and expected data from studies in two other indications, might influence future development plans.

Fearing Second Offer Failure, Stada Management Appeals To Shareholders
http://bit.ly/2uGpAhw
Stada's management is scared an offer from two private-equity suitors will fail a second time due to shareholder inactivity or reluctance to accept the deal before its Aug 16 deadline.

Merger With Cempra Takes Melinta Public, Will Help Launch Baxdela
http://bit.ly/2i3FdxM
In all-stock transaction, troubled Cempra will merge with privately held Melinta to create a fully integrated anti-infectives company.

inside:

Novo Nordisk: Semaglutide Heralds Commercial Dawn Of Obesity Market

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A rising tide lifts all boats. Denmark-based **Novo Nordisk AS** expects to benefit commercially - amid the surging obesity pandemic worldwide - from the eventual launch of its new GLP-1 agonist semaglutide, which studies show is very effective and safe in battling the condition.

And the anticipated success of the drug – which the company is moving into pivotal Phase III trials – should spur overall sector growth for treating obesity once launched, according to the group's Danish CEO.

"The obesity market needs to grow significantly. What will help unlock the obesity market, estimated at 600 million patients, is that we get products with higher efficacy, so we believe that a drug like semaglutide will help expand the growth of the market," CEO Lars Fruergaard Jørgensen told *Scrip* during a call with journalists.

Asked whether he was worried that semaglutide's success would cannibalize the company's current obesity treatment, the older GLP-1 agonist *Saxenda* (liraglutide), Jørgensen replied: "we are already the leader of the existing market based on Saxenda and when you are the market leader you're not chasing market share, you're chasing growth, and we believe semaglutide in obesity will help grow the market further."

The market for treating obesity is nascent, and its history is littered with failed treatments.

> 'What will help unlock the obesity market ... is that we get products with higher efficacy, so we believe that a drug like semaglutide will help expand the growth of the market'

STRONG SAXENDA SALES

Saxenda is more effective than past treatments. Launched in 2015 in the US, Saxenda has the same key ingredient as Novo Nordisk's diabetes blockbuster *Victoza* and works like a hormone that the body produces naturally that regulates appetite. Some doctors say they are comfortable with Saxenda because they have been prescribing Victoza for many years.

The company when releasing its results for the second quarter on Aug. 9 said the growth in Saxenda sales for treating obesity had been "very promising" and up 8% from the year-ago period, at DKK 686m ($109m). "What is really reassuring us is that we're not only seeing solid Saxenda growth in our core initial market, which was the US, but that the product is getting good traction in markets such as Latin America," said Jesper Brandgaard, Novo Nordisk's CFO.

He noted that Saxenda had been launched in Brazil around year ago for treating obesity. "That country is now the second largest market for Saxenda globally after the US. We generally see a keen interest in launching the product in a number of Latin American countries. We're also seeing strong interest for Saxenda in a number of Middle East countries where obesity is also a significant problem, and that's a region which has a relatively high ability to pay for that product," he said.

Semaglutide will lead commercial dawning of global obesity market, Novo Nordisk believes

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Physicians say a big problem in combating obesity medically is that patients often stop taking their prescribed drugs, and thus regain weight. New therapies like semaglutide may help people overcome that issue. Novo Nordisk CFO Brandgaard told *Scrip* that "we are also assessing whether the dose frequency in Phase III should be once daily or once weekly, so that is to also be defined in coming months."

SEEKS SEMAGLUTIDE SUPPORT IN DIABETES TOO

Semaglutide will also be a game changer in diabetes, Novo Nordisk believes. It hopes the therapy will help it claw back and keep bigger shares of an expanding diabetes market.

Novo Nordisk has seen its US market share slip recently amid increased pricing pressures and stiff competition to its once-daily Victoza from once-weekly products, notably **Eli Lilly & Co.**'s GLP-1 agonist *Trulicity* (dulaglutide).

"We believe Victoza will keep losing market share," CEO Lars Fruergaard Jørgensen conceded.

That's despite the cardiovascular benefit on the GLP-1 therapy's label which could help differentiate Victoza, because it will be the only GLP-1 with a proven cardiovascular benefit.

"Our real power play to hopefully stop the advance of Lilly's product is semaglutide," he added. "We believe that semaglutide will be differentiated enough from Trulicity that it will be a category on its own, because it will have the best efficacy on glucose regulation, on weight reduction, and also cardiovascular protective profile. It's a product that's therefore going to be sold on its profile, rather than on price," he said.

Data readouts from the Phase III SUSTAIN 7 head-to-head trial of semaglutide versus Trulicity are expected in the third quarter of 2017.

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Janssen's Sirukumab Faces Difficult US Commercial Path Even If It Clears Approval Hurdles

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A US FDA advisory committee found **Janssen Biotech Inc.**'s *Plivensia* (sirukumab) for rheumatoid arthritis stands out from competitors by concerns over a mortality signal, but not by any apparent efficacy advantages versus treatments already available.

The concerns about the mortality imbalance seen in clinical trials for the interleukin-6 inhibitor certainly make approval seem unlikely. However, even if the FDA were to clear sirukumab, such as for a narrower indication that drew more support from the panel, commercial prospects seem limited by lingering safety questions and an efficacy profile that advisory committee members said does not appear to stand out from other IL-6-targeting products or other biologic therapies used to treat rheumatoid arthritis (RA).

RA INDICATION SOUGHT

Janssen is seeking approval of sirukumab for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

The FDA's Arthritis Advisory Committee met Aug. 2 to discuss the biologics license application (BLA), but the review did little to boost sirukumab's chances of licensure by its Sept. 22 user fee goal date. The panel recommended against approval in a 12-1 vote. Although the committee unanimously endorsed sirukumab's efficacy, it voted 11-2 that the safety profile was inadequate to support approval.

Advisory committee members said they could not know for certain whether a mortality imbalance in the placebo-controlled trials was an artifact of the studies' design or a true safety signal. However, they seemed unwilling to take the chance that it might be the latter given the availability of numerous other biologic RA treatments that have not shown a mortality imbalance.

They also questioned the need for another IL-6-targeting agent in the absence of head-to-head data suggesting sirukumab might be better than the two IL-6 inhibitors currently on the market, **Roche**'s *Actemra* (tocilizumab) and **Sanofi** and **Regeneron Pharmaceuticals Inc.**'s *Kevzara* (sarilumab).

"We've got two other drugs that are [Il-6] inhibitors … but the [mortality] signals didn't appear there, and we have no suggestion of efficacy differences between this drug and those other two," said Steven Meisel, system director of patient safety at Fairview Health Services in Minneapolis. "If I was on a formulary committee, which I know this is not, this would be a no brainer. You wouldn't add it."

Some analysts seemed to agree that sirukumab's commercial prospects, which were handicapped to begin with, were further dampened by the advisory committee review.

"We had assumed relatively modest revenues for the product given its profile and its entry into a highly competitive market," Credit Suisse analysts said in an Aug. 2 note following the advisory committee meeting. "We decrease our probability of success for the product to 30%, lowering our global probability adjusted peak sales to less than $300m in 2026."

A NOT ENTIRELY NOVEL MECHANISM OF ACTION

Sirukumab is a monoclonal antibody that targets the IL-6 cytokine. Janssen said that while this mechanism of action overlaps with that of tocilizumab and sarilumab, which target the IL-6 receptor, sirukumab has the potential benefit of more selective inhibition of IL-6.

The mechanism of actions differs from that of Janssen's two currently marketed biologic RA treatments, *Remicade* (infliximab) and *Simponi* (golimumab), which are TNF inhibitors. Janssen has been successful thus far in protecting Remicade sales from biosimilar competition, but this may become more difficult as additional biosimilar versions of TNF inhibitors enter the market.

The proposed sirukumab dose is 50 mg given subcutaneously every four weeks. This dosing schedule would give Janssen's agent a competitive advantage relative to tocilizumab (dosed subcutaneously every week or every other week), and sarilumab (given subcutaneously once every two weeks).

Janssen is preparing to commercialize sirukumab on its own following partner **GlaxoSmithKline PLC**'s decision, announced one week before the advisory committee, to return rights to the biologic to the **Johnson & Johnson** division.

The primary efficacy evidence in the BLA is from two double-blind, placebo-controlled trials in the SIRROUND clinical development program.

Study ARA3002 was a 52-week, placebo-controlled trial in which patients were required to have had an inadequate response to DMARD therapy. The trial included escape points at weeks 18 and 40, at which time patients in the placebo arm who had less than 20% improvement from baseline in both swollen and tender joint counts could be re-randomized to one of the two sirukumab arms – 50 mg every four weeks (q4w) or 100 mg every two weeks (q2w).

Study ARA3003 employed a 24-week placebo control, and subjects were required to have had an inadequate response to one or more anti-TNF agents or intolerance to two or more TNF inhibitors.

The FDA did not raise any efficacy concerns about sirukumab. In both placebo-controlled trials, sirukumab was associated with a statistically significantly higher proportion of ACR20 responders at both doses relative to placebo. The estimated absolute increases in ACR20 response for the 50 mg q4w dose compared to placebo were 28% and 16% in the two studies.

In Study ARA3002, sirukumab also demonstrated a statistically significant effect on the primary radiographic endpoint of change from baseline in van der Heijde-modified Sharp score at Week 52.

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Clouded By Mortality Imbalance, read more here: **http://bit.ly/2uXivZo**

Real World Evidence's Commercial Facet

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Real world evidence (RWE) strategies when pursued and scaled across the product life cycle via a systematic approach can capture potential synergy/value of $1bn for a large pharmaceutical company, according to senior **QuintilesIMS** officials.

At a recent roundtable in Mumbai, Dr Ken J Lee, QuintilesIMS' chief medical officer, Asia Pacific, and head of medical and scientific solutions and real world insights in the region, discussed how extending RWE use to areas such as initial pricing and market access, launch planning and tracking and also commercial spend effectiveness can help realize a significant part of this value.

Lee explained that the $1bn represents "value capture" across the entire enterprise including commercial, which probably represents in the "order of 70-80% of the total opportunity".

Asked whether most pharma firms have underestimated the potential value of RWE on the commercial side given its domain is generally viewed as scientific, Lee told *Scrip* that he was seeing companies investing "heavily" in the area, but it is not the "norm" yet.

"The more aggressive companies are building extensive data sets from a variety of sources and investing in building technology data platforms to manage and analyze these data assets. Companies are clearly seeing the importance of real world evidence but need guidance on how to take advantage of the opportunity," he explained.

An IMS white paper from 2014 referred to a potential value capture from RWE of $150m in areas like launch planning and tracking and $200-300m in commercial spend effectiveness for a top 10 pharma company. Safety and value demonstration accounted for $200-600m in value gains.

While the scientific function is expected to be the data custodian and users of RWE for protocol-driven studies, the paper suggests that the commercial organization must "champion" RWE to broaden its value beyond traditional applications and realize its full potential. "The argument for commercial leadership of RWE capability planning and investment is two-fold. Firstly, the largest immediate financial value of RWE is in supporting about-to-launch and launched products, areas for which commercial drives decision making. Many decisions related to labeling and identifying target patients, contracting and pricing strategies, and launch planning are transformed by RWE, requiring that commercial be close to RWE strategy," the 2014 paper on RWE said.

The roundtable also heard how patient data reflects a "seismic shift" in evidence evaluation and that the RWE ecosystem will be fueled by supply and demand. On the supply side, among others, there are increasing patient-level data and analytical technologies, an explosion in the volume of electronic patient data and new stakeholders conducting analysis, which in turn creates more data. Factors driving demand included increasing cost pressures and new treatments to fund.

COMMONLY USED IN REIMBURSEMENT DECISIONS

But despite all the attention and opportunities around RWE, regulators generally appear to be treading cautiously in the area, at least for now.

Asked whether RWE is yet to emerge as a widespread regulatory reality, especially in markets like the US and Europe, Rauf Mohamed, senior principal at QuintilesIMS, noted that while RWE is not always a mandatory requirement for product registration in most markets, it is very commonly used when reimbursement decisions are made.

"Recent evaluation of NICE submissions has revealed that RWE drives HTA approval in 86% of submissions. Regulatory authorities may also ask for commitment to post-marketing safety studies as a condition to product registration/approval," Mohamed told Scrip.

He added that pharmacovigilance is a mandatory requirement from several regulatory authorities and that, in most cases, is based on real-world data.

"So, in effect, real world evidence is being used in different forms by regulatory authorities."

RWE AND THE MIDDLE EAST

Mohamed, with significant expertise on the Middle East, also noted how with reducing oil prices, there has been an increasing focus on optimizing healthcare expenditure. In that context, real world evidence is being recognized and used as an important tool to inform policy building and define practical budget allocations in the region.

"The Arab network of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has been talking about introducing HTA guidelines for the region, and although this is still work in progress, the significance applied to RWE is evident in the increasing research activity that is taking place," he explained to *Scrip*.

He maintained that certain regulatory authorities in the region are also asking for "commitment" to post-marketing safety studies as a condition to product registration/approval.

"There have been expectations that this could become the norm especially for highly prevalent chronic disease areas, but we are yet to receive guidance on that," he added.

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Celgene Revamps IO Deal With Emerging Biotech Sutro

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The restructuring of a 2014 discovery and development deal for immuno-oncology assets means **Celgene Corp.** no longer has the option of acquiring its small biotech partner, **Sutro Biopharma Inc.**

In what the two firms have called a "refocus," restrictions have also been lifted that previously prevented Sutro agreeing additional collaborations with other partners or accessing the public financial markets.

Celgene and Sutro redraft 2014 IO deal

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In May this year, Sutro CEO Bill Newell told *Scrip*'s sister publication *In Vivo* that it and Celgene had an extensive list of projects under its IO alliance. "Sutro built a platform that is agnostic to biology, which is why we wanted to marry up with Celgene, which has the know-how to help us specify targets to explore for maximum therapeutic impact on patients," Newell said, adding that "together, we have identified an extensive list of projects – more than 15 in all – of drug candidates for potential commercialization."

As part of their alliance revamp though, Celgene and Sutro said they would now concentrate on just four key preclinical assets.

As part of the original collaboration agreement, initiated in 2014, Celgene has worldwide rights to the first collaboration program to reach investigational new drug (IND) status.

Under the modified agreement, announced Aug. 10, Celgene can acquire worldwide rights to a second program to reach IND status. Meanwhile, Sutro will retain US development and commercialization rights, and Celgene will keep ex-US rights, to the last two programs to reach IND status from the four programs in the partnership.

The revised agreement sees Sutro receive an undisclosed payment from Celgene; the biotech also continues to be entitled to development and regulatory milestone payments and royalties related to the immunotherapy drug candidates.

The four programs at the center of Sutro's deal with Celgene are all in the preclinical setting and they include an antibody drug conjugate (ADC) program targeting B-cell maturation antigen (BCMA).

As well as these assets in development with Celgene, Sutro's early-stage oncology pipeline also includes two 2018 IND candidates: STRO-001, an ADC targeting CD74 that has potential in areas like non-Hodgkin's lymphoma and multiple myeloma; and STR0-002, an ADC which targets folate receptor alpha which is overexpressed in platinum-resistant ovarian cancer and other solid tumors. Sutro is also advancing six ADC programs under a 2014 collaboration with **Merck KGAA**.

NO TAKEOVER OPTION

An important change in the revised deal, Celgene's option to acquire Sutro has been terminated along with restrictions that previously prevented Sutro entering into additional collaborations or accessing the public financial markets.

The acquisition option in Celgene and Sutro's alliance was always due to be reviewed before the end of Sept. 2017.

Despite no buyout offer being on the cards, Sutro has granted Celgene the right to purchase shares of its stock in a future private financing rounds and the right to purchase shares if the company launches a public offering.

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MyoKardia Shares Promising Cardiac Data

It was only 10 patients but the topline data **MyoKardia Inc.** unveiled on Aug. 7 for its Phase II cardiomyopathy candidate mavacamten had a big impact on the biotech's stock. The company's share price soared 83% on the day and market analysts suggested there could be an opportunity for accelerated clinical development and potential breakthrough therapy designations.

MyoKardia is partnered on the drug with **Sanofi**, one of its initial investors via the French pharma's Sunrise open innovation initiative. Sanofi paid $45m up front ($10m an equity stake) in 2014 for ex-US rights to mavacamten, as well as global rights to MYK-491.

The South San Francisco, Calif.-based firm reported that mavacamten (MYK-461), a novel, oral allosteric modulator of cardiac myosin, met the primary endpoint and several secondary measures in its Phase II PIONEER-HCM trial in patients with symptomatic, obstructive hypertrophic cardiomyopathy (HCM). On a same-day investor call, CEO Tassos Gianakakos said MyoKardia hopes to work out a plan with the FDA in the coming months to make the planned EXPLORER-HCM study a pivotal trial for the candidate.

Of 11 patients enrolled in PIONEER, 10 completed 12 weeks of treatment with all achieving a reduction from baseline in post-exercise peak left ventricular outflow tract (LVOT) gradient. Further, eight of the 10 achieved a reduction in that measure equivalent to below the diagnostic threshold for obstructive HCM. A key secondary endpoint of peak oxygen consumption (peak VO2) also was met.

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7 August 2017

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Benlysta Is Niche, But Growing, So GSK's Not Giving Up On Lupus

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GlaxoSmithKline PLC launched a new subcutaneous formulation of *Benlysta* (belimumab) in August that could make the drug easier to use for some patients with systemic lupus erythematosus (SLE) than the original intravenous version. The US FDA approved the new formulation, administered as a once-weekly 200mg injection, on July 22.

Benlysta probably is best recognized by industry watchers as the blockbuster that never was. GSK and its then-partner **Human Genome Sciences Inc.** launched Benlysta in 2011, when it was hailed as the first new drug for the treatment of lupus in 50 years. *(Also see "HGSI/GSK's Benlysta Gets BLySfully Clean Labeling, Escaping Feared Restrictions" Pink Sheet, 10 Mar, 2011.)* Some analysts at the time were forecasting that sales would reach as much as $5bn by 2016, given the unmet need in the market *(Also see "HGSI/GSK's Benlysta Gets BLySfully Clean Labeling, Escaping Feared Restrictions" Pink Sheet, 10 Mar, 2011.)*

Benlysta fizzled out of the gates and never got on a blockbuster footing, with one of the biggest challenges being the drug's modest efficacy, as well as discrepancies over the actual size of the commercial market. GSK took advantage of the dip in HGS's stock price to buy out the company in 2012 for $3.6bn, an amount that now seems like a very good deal for the biotech's investors. *(Also see "HGSI Gets Slightly Increased Buyout Bid, Accepts GSK Offer Of $3.6 Billion" Pink Sheet, 16 Jul, 2012.)*

But GSK hasn't given up on Benlysta. Six years post-launch, the company continues to invest in clinical trials to expand indications and better understand the benefits of belimumab in patients with lupus. The company has had to reset expectations from blockbuster to niche level, but Benlysta has been growing by double digits every year since launch. Sales of Benlysta in 2016 were £277m ($361.5m), up 18% year-over-year. In the first half of 2017, sales increased 29% to £184m.

"Immuno-inflammation is one of our core therapeutic areas of focus, and lupus is our foundational pillar in that area," Tania Gonzalez-Rivera, a rheumatologist on the company's medical affairs team, said during an interview.

"With the approval of the subcutaneous form of Benlysta we will be able to provide physicians and patients options and the possibility of self-administering their medication in the comfort of their own home," she said. A self-administered formulation may be especially welcome for lupus patients, who are generally young, active women. The IV version is administered by a health care professional as a one-hour infusion, every four weeks.

LUPUS PREVALENCE UNCLEAR

Part of the commercial reset for Benlysta involved better understanding of the number of patients appropriate for treatment, added VP-immunology/rare diseases Sheri Mullen.

"There are 200,000 patients who are actually diagnosed, according to claims data, with SLE in the US, and 100,000 are appropriate patients for Benlysta," she said. "It isn't for all lupus patients."

Many more patients may be living with lupus, but are undiagnosed, with estimates by the Lupus Foundation of America running up to 1.5m patients. Still, the number of patients likely to be treated with a biologic drug is much smaller. GSK said the number of patients diagnosed with lupus is much smaller.

"A big disparity is what is actually diagnosed, 200,000 SLE patients, to what you hear, and I sometimes think that set the expectation at launch," Mullen said. Lupus specialist Richard Furie, chief of the division of rheumatology at Northwell Health, agreed. He said the number of patients diagnosed with lupus is around 300,000 patients, including patients with lupus nephritis, the type of lupus that affects the kidneys and can lead to kidney failure. "This is what confused the investment community," he added.

One issue for Benlysta, he said, is "the rheumatology community is polarized about how effective it is." Some rheumatologists believe it is only modestly effective and not worth the cost, partly stemming from confusion over the clinical trial endpoint that was used in the trial. Furie, however, said he has a positive view of the drug and while it is not a super potent drug, it has a positive impact on patients in the maintenance setting in terms of reducing flares.

The original approval was based on two Phase III studies that relied on a novel and unvalidated composite endpoint known as the SLE Responder Index. *(Also see "FDA's **Benlysta** Approval: A Lesson In Overcoming Unvalidated Endpoints" Scrip, 1 Jun, 2011.)* The endpoint grew out of HGS' exploratory analysis of a failed Phase II trial, which relied on a different endpoint, percent change in the SELENA-SLEDAI disease activity score, and thus, some uncertainty hung over the new endpoint.

Benlysta is a BLyS-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B cells. It does not bind B cells directly, but by binding BLyS, Benlysta inhibits the survival of B cells, including autoreactive B cells. Lupus occurs when patients' antibodies produced by B cells, mistakenly attack the body's own cells, so depleting B cells is one approach to treating the disease.

The trial for the subcutaneous formula used the same endpoint used in the IV pivotal studies. The subcutaneous approval was based on the results of a

double-blind, placebo-controlled trial involving 836 patients with SLE, and evaluated Benlysta 200 mg once-weekly plus standard therapy compared with placebo once-weekly plus standard therapy over 52 weeks. The primary efficacy endpoint was the SLE Responder Index-4 (SRI-4) at Week 52. The proportion of patients achieving an SRI-4 response was significantly higher in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (61% versus 48%).

PRICED AT PARITY

The wholesale acquisition cost for Benlysta subcutaneous is $3,530 for a one-month supply, a pack of four pens (four single-dose autoinjectors or pre-filled syringes). GSK worked to price the new formula on par with the intravenous formula on a per milligram basis, the company said, given differences like dosing, frequency and administration. The intravenous formulation is dosed by weight, while the subcutaneous version is not.

The company expects there may be some access challenges initially, given that the subcutaneous version will be reimbursed through the pharmacy benefit rather than the medical benefit, as the IV version is.

"Right out of the gate, we won't have the same access that we have with Benlysta IV and we will have to submit for individual pharmacy coverage for the payers. That usually takes up to a year depending on their review cycle," Mullen said.

GSK is running several other large trials with Benlysta in lupus, including a trial exploring mortality and adverse events, another studying African-American patients and one testing patients who take a treatment-holiday trial. The company also is exploring Benlysta in combination with *Rituxan* (rituximab)

"We are committed to the ongoing studies, to answering the many unanswered questions in this complicated disease," Mullen said.

GSK has committed to immuno-inflammation as a core R&D area, with Benlysta as an anchor product, even as new CEO Emma Walmsley unveiled an R&D overhaul July 25. *(Also see "Walmsley Shakes Up GSK; Cuts More Than 30 Drug Development Programs" Scrip, 26 Jul, 2017.)*

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CONTINUED FROM COVER

SLE in 50 years. At the time of the launch, some analysts forecast that Benlysta would become a $5bn product, given the significant patient numbers and unmet need.

In reality, the ambitious forecasts never materialized, and today, Benlysta remains a niche product. Sales of Benlysta were £277m ($361.5m) in 2016, up 18% over 2015. In the first half of 2017, sales increased 29% to £184m ($240m). The double-digit growth is notable and GSK continues to invest behind the brand, including the recent launch of a new subcutaneous formula.

There are a lot of takeaways from the Benlysta experience. Benlysta is perceived as having moderate efficacy and was approved by the FDA with a novel endpoint that physicians weren't familiar with, both of which may have limited uptake. But stakeholders largely agree lupus should be a blockbuster commercial opportunity.

"We estimate that lupus is a $3bn-$5bn market, especially when you include lupus nephritis," AstraZeneca's Nohe said. AstraZeneca is ahead in the field, with anifrolumab in Phase III testing for moderate-to-severe SLE.

The Lupus Foundation of America's Raymond insisted lupus absolutely is a blockbuster commercial opportunity for drug manufacturers. "Even if you have 100,000 patients and a $20,000 to $30,000 drug, you have a market of $3bn," she maintained.

Genentech Inc.'s global head, rheumatology and rare diseases, product development-immunology Jeffrey Siegal declined to comment on the commercial potential, but stood by the opportunity. "Our understanding from current data is that lupus is not uncommon," he said. "There are an estimated 1.5m people who have lupus. It's true that the number of patients with serious conditions, ones that might benefit from a targeted therapy such as many of the ones being developed now, is a smaller fraction of that. We think, nonetheless, there is high unmet medical need."

QUESTIONS LINGER

The Lupus Foundation of America believes the number of patients with lupus in the US is around 1.5m, but the prevalence of the disease remains a question. The foundation based its prevalence rates on two epidemiologic studies funded by the association, and Raymond acknowledged it includes patients with all types of lupus, including cutaneous lupus.

"We are going to stay with our number, because it is a number that we tested over and over again," Raymond said.

Nonetheless, the number of patients diagnosed with SLE is considerably lower, just several hundred thousand patients in the US, according to several experts.

Lupus specialist Richard Furie, chief of the division of rheumatology at Northwell Health in New York and a chief investigator in several lupus trials, said around 300,000 patients in the US are diagnosed with lupus, including 50,000 with lupus nephritis. AstraZeneca said the company believes there are over 600,000 patients in the G7 markets diagnosed with lupus, including 400,000 in the US.

For GSK, the lesson was a hard one to learn. The company places at least some of the blame for the disappointing Benlysta launch on confusion over disease prevalence, which resulted in bloated forecasts for the drug. Part of the commercial reset for Benlysta involved better understanding the number of patients appropriate for treatment, VP-immunology/rare diseases Sheri Mullen said.

"There are 200,000 patients who are actually diagnosed with SLE in the US, and 100,000 are appropriate patients for Benlysta," she said. "It isn't for all lupus patients."

"A big disparity is what is actually diagnosed, 200,000 SLE patients, [versus] what you hear and I think that sometimes set the expectation at launch," Mullen said.

But given the unmet medical need in a disease that affects mainly women in their prime, there most certainly remains a lucrative commercial market for the right drug – one that can demonstrate substantial efficacy safely. There are a wide range of drugs now in clinical development exploring multiple pathways in various subtypes of the disease, building off the knowledge that led to the approval of Benlysta. Nonetheless, Benlysta shows first-hand that modest efficacy isn't enough to establish a blockbuster in lupus.

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[Editor's note: The state of the pipeline for lupus nephritis and SLE will be reviewed in an upcoming article.]

Mylan Preparing Response To Generic Advair CRL, And It Needs A Win

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Mylan NV aims to get its application for a generic version of **GlaxoSmithKline PLC**'s asthma blockbuster *Advair Diskus* (fluticasone/salmeterol) back in the US FDA's court soon. During the company's second quarter earnings call on Aug. 9, president Rajiv Malik said the company would be ready to respond to the complete response letter received from the FDA "in the next couple of weeks."

The update on the important application comes after Mylan met with the FDA to discuss the CRL and clarified that it will not need to conduct further clinical trials or device-related studies to address the FDA's concerns.

"We were pleased with the highly constructive nature of our dialogue with the agency, and we were able to clarify and resolve a number of key points raised in the CRL," Malik said.

Mylan, nonetheless, has removed an Advair generic from its 2017 guidance, but Malik said the agency continues to view the application as a high priority. "We continue to be ready from both a manufacturing, as well as a commercial, perspective to launch upon approval," he said.

Mylan could use a win on Advair generic or another high-profile opportunity. The company has positioned itself as a leader in complex generics and biosimilars to navigate through the challenging small molecule generic market, and while it has invested considerably in R&D, it is yet to show it can get the drugs across the finish line and onto the market.

Mylan was the first company to file a generic version of Advair with the FDA last year, positioning the company to secure a leadership position in what is expected to be a lucrative market. Advair generated £3.49bn (about $4.34bn) worldwide in 2016. But Mylan received a complete response letter from the FDA in March, delaying the approval likely into 2018 at the earliest. *(Also see "Mylan's Generic Advair Delay Gives Leverage To Rivals" Scrip, 29 Mar, 2017.)* A second application sponsored by **Hikma Pharmaceuticals PLC** was also met with a CRL by the FDA.

DEFERRING MAJOR US LAUNCHES UNTIL 2018

Advair is one of two complex generics Mylan is hoping to secure the FDA's approval for in the near term. The other is a generic version of **Teva Pharmaceutical Industries Ltd.**'s multiple sclerosis drug *Copaxone* (glatiramer), both the 20 mg and 40 mg dose. Mylan's application for generic Copaxone also appears to be hung up at the FDA.

During the earnings call, Malik warned investors to expect a further delay. "Regarding Copaxone, we are disappointed with the execution by the FDA of this complex ANDA as the administrative timeline continues to move despite a number of interactions, as well as meeting all of the criteria for the product-specific guidance issued by the FDA," he said. The company does not anticipate having to conduct additional clinical trials.

But the delays raise issues about the FDA's process for reviewing complex generics, according to Mylan, and also impacted the company's financial forecast for 2017.

"Given this unpredictability and in an abundance of caution, we have removed Copaxone and Advair from our 2017 financial guidance and have simply deferred them to 2018," CEO Heather Bresch said. The company said it would push back all major US launches into 2018. As a result, Mylan said it now expects to deliver revenues of $11.5bn to $12.5bn for the year and adjusted earnings per share of between $4.30 and $4.70. The company previously forecast revenues of $13.25bn to $13.75bn, and EPS of $5.15 to $5.55.

At the same time, while Mylan has been hit with delays for high priority complex generics, the company has also been affected by more ANDA approvals across the board at the FDA, flooding the market with more competition and putting pressure on US generic drug prices. The issue is one that has hit generic drug manufacturers across the spectrum, along with buyer consolidation. The US market has been a significant challenge for generic drug manufacturers in 2017. *(Also see "Generic Manufacturers Try To Up Their Game As US Pressure Persists" Scrip, 16 Jun, 2017.)*

The FDA has made reducing its ANDA backlog a top priority and has largely succeeded, but those drugs tend to be generics that are the third, fourth, or fifth to market. The agency, under new the FDA Commissioner Scott Gottlieb, has also talked about prioritizing certain generics.

The company is having a hard time squaring the delays for complex generics with the FDA's overall faster review of ANDAs in the minds of some investors, especially given the company's enormous pricing scandal and setback with *EpiPen* last year, when it agreed to launch a generic version and cover more out-of-pocket costs for patients. In March, the company said EpiPen would have a negative $400m impact on Mylan in 2017.

Looking to put the 2016 challenges behind it, Mylan tried to lay out a positive growth story for the company during an investor day on March 2. Management pointed to the company's focus on complex generics and biosimilars and its geographic diversification. *(Also see "Mylan's Growth Strategy: Diversification, Expansion And R&D Investment" Scrip, 2 Mar, 2017.)* But the company's stock is down 29% since the March 2 meeting, closing on Aug. 9 at $32.08.

"I assure you, given our depressed share price, I'm very focused on continuing to engage and educate investors about the true value of Mylan's unique and highly differentiated platform," Bresch said during the call.

A string of acquisitions has helped Mylan's top-line. Total revenues in the second quarter were $2.96bn, up 15% from the prior quarter. But third-party net sales in North America declined 9% to $1.28bn, with the drop attributed to US price erosion in the mid-single digits and lower sales of EpiPen as the result of authorized generics and higher accrued government rebates. GAAP net earnings increased by $129.6m to $297m in the quarter, with the gains coming from $50m in litigation settlements and another $88.1m gain coming from a fair value adjustment related to the respiratory delivery platform.

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FibroGen Hails 'Milestone' IPF Data, Phase III And Partners Beckon

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FibroGen Inc. appears to have a potential blockbuster on its hands with its anti-connective tissue growth factor (CTGF) antibody pamrevlumab (FG-3019) after Phase II data suggested its potential as a monotherapy and possibly in combination with current treatments for idiopathic pulmonary fibrosis, a disease which has a poorer prognosis than many cancers.

The data suggest that as a monotherapy the drug produces a similar reduction in the rate of disease progression as currently marketed therapies – nintedanib (Boehringer Ingelheim's *Ofev*) and pirfenidone (Roche's *Esbriet*) – but with a hint of a mortality benefit that could set it apart. Sub-studies, meanwhile, showed that the novel product can be used safely in combination with the established products.

"We view these data as an important milestone for the company and for the program, and we believe the results of this study enable us to move into Phase III with IPF," FibroGen founder and CEO Thomas B. Neff told a conference call. The company is now set to meet the US FDA to address the clinical and regulatory path forward for pamrevlumab in this indication.

Observers had previously been skeptical of its potential in this indication, and its fresh commercial prospects sent FibroGen shares up by more than 50% to around $50 on NASDAQ the morning of August 8; the drug is also in development for pancreatic cancer and Duchenne muscular dystrophy. FibroGen's other main pipeline hopeful is roxadustat, the leading HIF (hypoxia-inducible factor) prolyl-hydroxylase (PH) inhibitor in Phase III in chronic kidney disease patients; the product is licensed to Astellas and **AstraZeneca PLC**.

Neff believes IPF will be a significant value generator for pamrevlumab because of the severe unmet medical need and limited life expectancy at the time of the diagnosis. "Pamrevlumab may represent a valuable option to treat IPF patients as our results suggest improvements in both standard measurements in lung function, improved safety and quantitative measurement of fibrosis." Since the drug is being developed for a number of indications, the company also would like a partnership that "is anticipating the breadth of opportunity both in straight fibrosis and in the cancer arenas, where fibrosis is important and in combination with things like the PD-L1 medicines".

'The approximate 50-60% improvements are in line with two other approved drugs, Roche's Esbriet and Boehringer's Ofev'

STUDY DETAILS

In the 103-patient placebo-controlled study pamrevlumab (30 mg/kg iv every three weeks for 48 weeks) met the primary efficacy endpoint of change of forced vital capacity percent predicted (FVC % predicted) from baseline to week 48 of the study. FVC1% predicted is a measure of change in lung volume that takes into consideration the person's age, sex, and body composition.

Using a linear slope analysis in the intent to treat population, the average decline in FVC % predicted from baseline to week 48 was 2.85 in the pamrevlumab arm compared with 7.17 in the placebo arm, an absolute difference of 4.33. "Thus, the relative decline was 60% less than placebo with a p-value of 0.0331," said chief medical officer Peony Yu.

Pamrevlumab-treated patients had an average decrease in FVC of 129 ml at week 48 compared with an average decrease of 308 ml in patients receiving placebo, another statistically significant difference. The product was also well tolerated, and was associated with numerically fewer deaths: there were three deaths in the pamrevlumab arm compared with six with placebo, making the treatment arm deaths about half that predicted. FibroGen also performed two sub-studies using current therapies as background treatment (*Ofev* and *Esbriet*) in 57 patients, from which the safety data were also reassuring, but no efficacy data from these were released. The company said additional analyses would be presented at the European Respiratory Society meeting in Milan on September 12.

SKY HIGH

The proof-of-concept results mean FibroGen is in the pleasant position of having two products either in or approaching Phase III.

Analysts from Jefferies believe investors or a potential global partner interested in the pulmonary or orphan disease space could ascribe a value to the product in the order of $2-4bn plus for IPF and pancreatic cancer, given that positive Phase II data are reasonably likely to repeat in Phase III based on mechanism, plus the significant unmet medical need, and the potential for combination therapy and possibly longer treatment durations than with existing products.

"The approximate 50-60% improvements as monotherapy are at least in line with two other oral drugs already approved, Roche Esbriet and Boehringer's Ofev, which as a class are on pace to be multi-billion in sales and [FibroGen's drug] would be mono or added on top," they said.

Analysts at Leerink were similarly impressed with the new data. "We previously afforded pamrevlumab 0% probability-of-success (PoS) in our model given prior development delays and some disappointments; based on the compelling proof of concept Phase II results we are increasing that to 35% PoS, which contributes $392m in worldwide sales in 2022E growing to $892m to 2025E."

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New Beginnings – How Trials Started In 2016 Are Shaping The Clinical Landscape

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More than 6,000 clinical trials investigating at least one drug were begun in 2016, with just over half testing an unapproved primary drug, new research from Trialtrove reveals. The findings show cancer's growing dominance in pharmaceutical R&D and reveal which specific oncology indications were the most popular for new trial starts last year.

Of the 6,067 Phase I-III clinical trials initiated in 2016 that investigated at least one drug, 57% (3,484) were testing a product that has yet to receive regulatory approval. 2,442 were testing cancer therapies – more than three times the number of trials starts for the next most prolific area, CNS, which had 854 trial initiations (see Figure 1).

As anticancer products comprise the largest portion of the R&D pipeline, with nearly twice as many as neurological drugs (the second largest disease-specific therapy group), it is likely that cancer trial activity will continue to rapidly proliferate, the report says.

Changing the landscape

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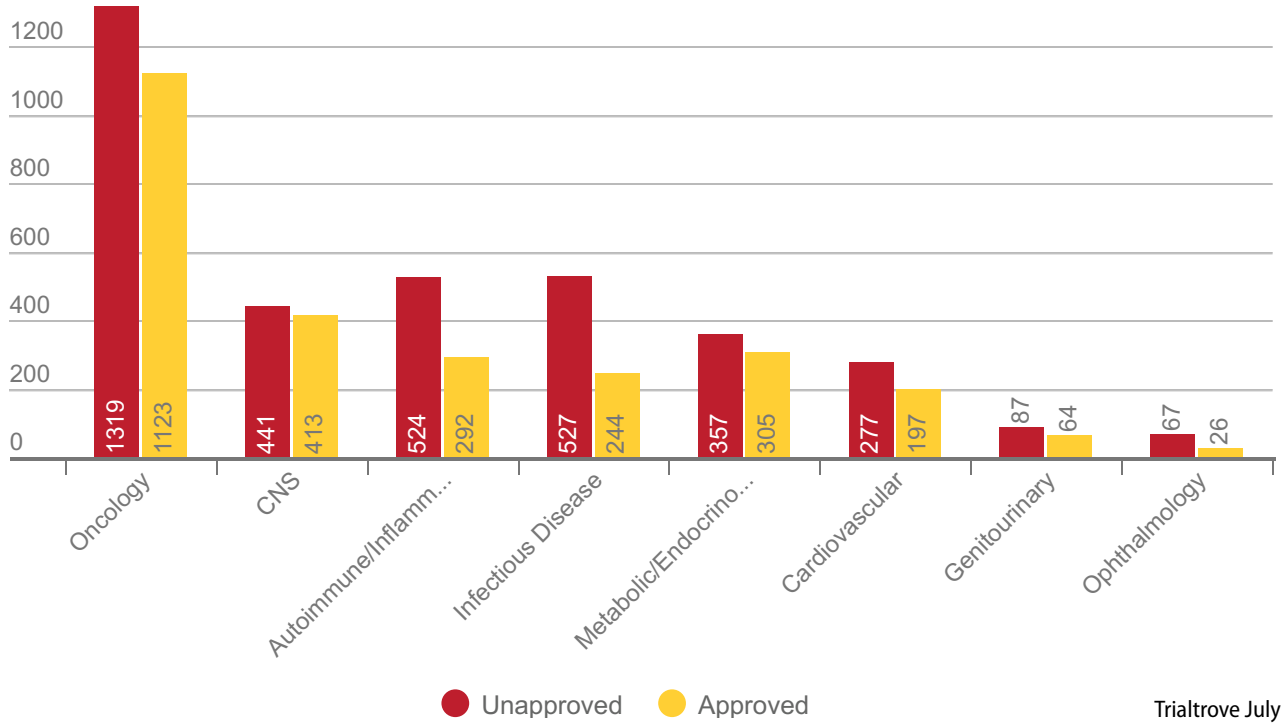
For all therapy areas, trials with investigational drugs outnumber those focusing only on already approved drugs. Those therapy areas with the largest proportion of trials of already approved drugs (around half) were oncology, CNS and metabolic, suggesting that these are the areas where label expansions are being most assiduously sought. By contrast, the proportion of studies of already approved drugs was about a third for autoimmune/inflammatory disorders (A/I) and infectious diseases (ID), and for ophthalmology it was the lowest at 28%, suggesting a higher level of innovation in this area, the report found.

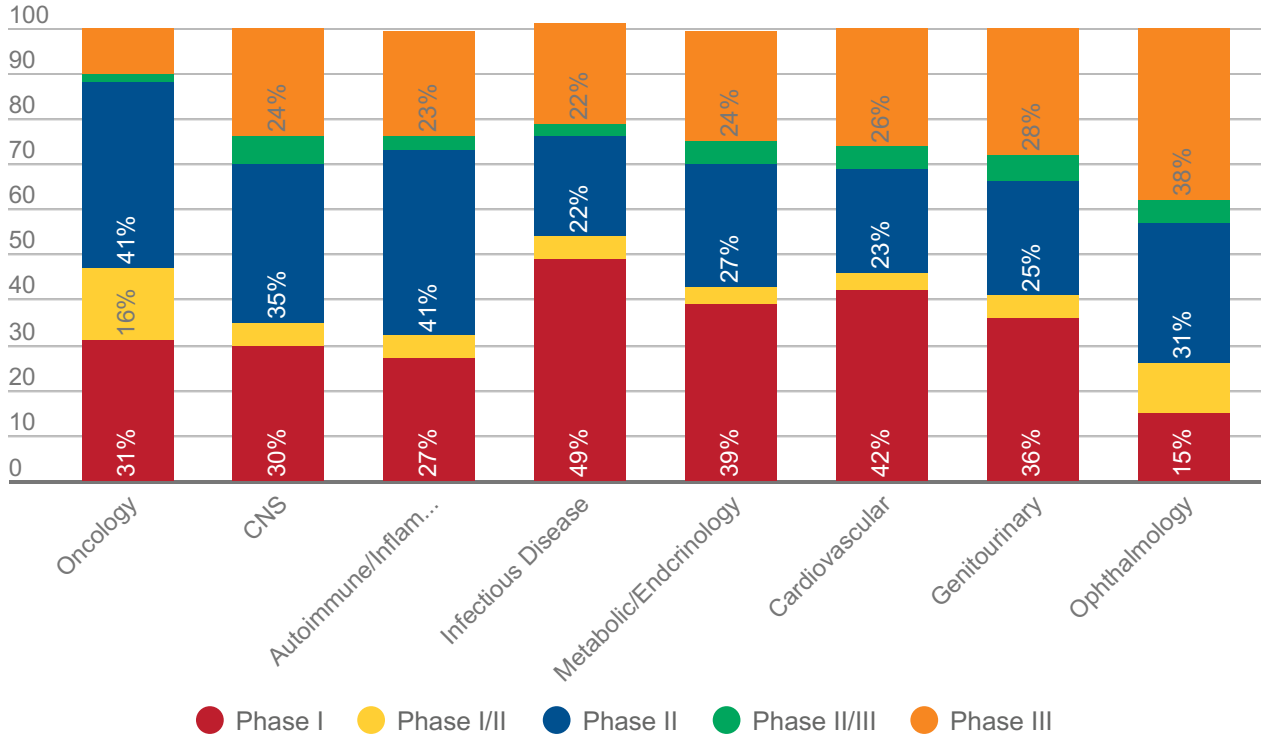
Editor's note: 2017 marks the launch of the next generation Clinical Trials Roundup from Trialtrove. It expands on overviews produced

Figure 1: Phase I-III Clinical Trials Started In 2016 By Drug Status



Trialtrove July 2017

Figure 2: Distribution Of Phase I-III Clinical Trials Started In 2016 By Phase



NB: percentages may not add up due to rounding

Trial Counts By Phase	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Total
Oncology	756	384	1,009	40	253	2,442
CNS	259	46	296	51	202	854
Autoimmune/Inflammation	220	43	338	26	189	816
Infectious Disease	375	38	166	26	166	771
Metabolic/Endocrinology	261	28	181	32	160	662
Cardiovascular	199	21	108	22	124	474
Genitourinary	54	8	37	9	43	151
Ophthalmology	14	10	29	5	35	93
Total	2,083	560	2,089	195	1,140	6,067

Trialtrove July 2017

in the past by being more inclusive – it moves beyond unapproved drugs within Trialtrove's six major therapeutic areas of autoimmune/inflammation (A/I), cardiovascular (CV), CNS, infectious disease (ID), metabolic/endocrinology, and oncology, to include trials supporting market or label expansion endeavors, as well as the smaller, but not insignificant, therapy areas of genitourinary and ophthalmology. Since this year's dataset is more inclusive, and has a later snapshot date than years past, it is less helpful to make comparisons with previous years.

THERAPY AREAS

The most active therapy areas – oncology, CNS, and A/I – were largely driven by new Phase II activity, followed by Phase I. Oncology was particularly weighted toward early to mid-stage clinical development, with only 10% of its new anticancer trials in Phase III. But because of the sheer volume of cancer studies, this therapy area still takes first place for number of Phase III starts overall (see Figure 2).

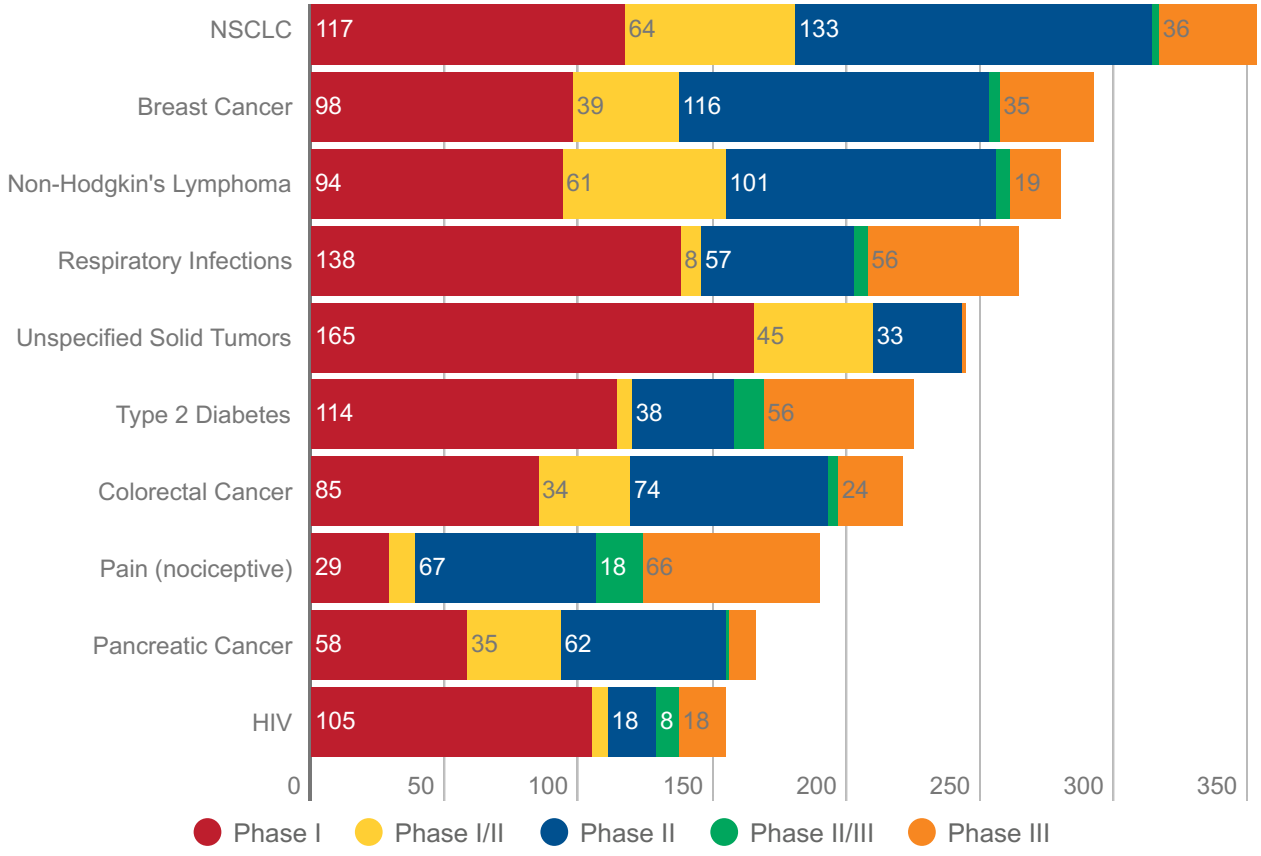
The study starts in the remaining therapy areas tended towards the earlier phases – Phase I comprised between 36% and 49% of trials for infectious diseases, metabolic, cardiovascular, and genitourinary.

Phase III study starts comprised similar proportions across the CNS, AI, ID, metabolic/endocrinology, CV and genitourinary areas – between 22 and 28%. But ophthalmology bucked the trend again with 38% of its new studies being Phase III and a further 5% at Phase II/III.

Overall, trial hybrids were generally uncommon, the report found, but Phase I/II

CONTINUED ON PAGE 14

Figure 3: Top 10 Diseases Of Phase I-III Clinical Trials Started In 2016 By Trial Count



Trialtrove July 2017

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studies were more frequent for ophthalmology, as well as oncology, reflecting the earlier movement of drugs into patients to evaluate proof of concept or initial efficacy while still establishing safety in these therapy areas.

SPECIFIC DISEASES

As expected, the most popular specific disease indications for the new trial starts were cancers, with three oncology indications taking the top places, and 12 out of the top 20 spots overall. Non-small cell lung cancer (NSCLC), breast cancer, and non-Hodgkin's lymphoma headed the table, with unspecified solid tumors taking fifth place. The few diseases outside of oncology spanned a range of therapy areas, led by respiratory infections at fourth place, followed by type 2 diabetes at sixth, and nociceptive pain at eighth. HIV came in at tenth place.

Anticancer products comprise the largest portion of the R&D pipeline

At the early end of the pipeline, unspecified solid tumors accounted for most new trials, "signaling the industry's ongoing battle with solid tumors", the report found. For most indications, the bulk of trials initiated in 2016 were in Phase I. Seven had the most activity in Phase II, including the three cancers at the top of the pack, while none had Phase III as the largest proportion of trials. Nociceptive pain, however, was close, with only a single study difference between Phase II and Phase III, and does appear to be the largest single disease target for late-stage development (see Figure 3).

MORE DETAILS

The full 2016 Clinical Trials Roundup: The Next Generation white paper is available from Trialtrove.

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Phase III Lasmiditan Data Strengthens Lilly's Dual Migraine Strategy

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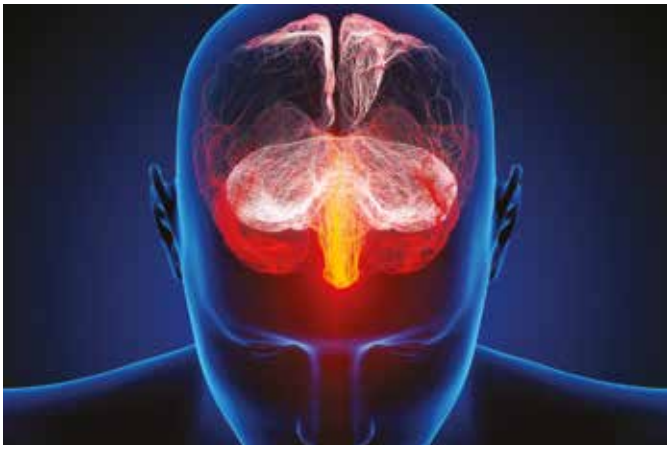
Eli Lilly & Co. will seek the US FDA's approval for lasmiditan in the acute treatment of migraine headaches in the second half of 2018 – about a year after submission of galcanezumab for the prevention of episodic and chronic migraine – based on the oral drug's success in a second Phase III clinical trial.



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The company bought **CoLucid Pharmaceuticals Inc.** for $960m earlier this year to reclaim the Lilly-discovered lasmiditan for its growing pain portfolio, which includes the CGRP inhibitor galcanezumab. *(Also see "Lilly Pays Nearly $1bn To Regain Migraine Candidate It Once Sold For $1m" Scrip, 18 Jan, 2017.)* Lasmiditan gives the company an oral therapy to stop headaches that break through the prophylactic effects of its biologic galcanezumab – a commercial advantage that could be important given the increasingly competitive nature of the migraine market for new branded drugs.

Lasmiditan is designed to target 5-HT1F in the trigeminal pathway without vasoconstrictor activity observed for other migraine therapies. Patients with one or more cardiovascular risk factor or known coronary artery disease were not excluded in the Phase III SAMURAI trial, which CoLucid successfully completed last year, nor in the Phase III SPARTAN trial for which Lilly reported results on Aug. 4.

In both studies, the drug was tested in patients with five migraine headaches or more per month and who had at least moderate migraine disability as measured by a Migraine Disability Assessment Score (MIDAS) of at least 11.

In SPARTAN, lasmiditan met the primary endpoint of the percentage of patients who were migraine pain-free two hours after taking a dose of the drug: 28.6% for the 50 mg dose (p=0.003), 31.4% for 100 mg group (p<0.001), 38.8% for 200 mg (p<0.001) and 21.3% for placebo.

A secondary endpoint looked at the percentage who were free of their migraine-associated most bothersome symptom – defined as nausea, sensitivity to light or sensitivity to sound – two hours after taking lasmiditan: 40.8% for the 50 mg dose (p=0.009), 44.2% for 100 mg (p<0.001), 48.7% for 200 mg (p<0.001) and 33.5 % for placebo.

"Based on these clearly positive results in a second Phase III pivotal trial, we are raising the [likelihood of approval (LOA)] of lasmiditan for the acute treatment of migraine by another 3%," Biomedtracker said in an Aug. 4 report. "Lilly initiated two Phase I [pharmacokinetic] single-dose studies of lasmiditan in subjects with normal and impaired hepatic function and with normal and impaired renal function in March 2017. If these trials are also positive, there will likely be a clear path to the FDA approval in 2019."

The most common adverse events in SPARTAN, which enrolled 3,007 patients, were dizziness, paresthesia, somnolence, fatigue, nausea and lethargy. A 2,580-patient open-label Phase III study called GLADIATOR is ongoing to test long-term safety of the 100 mg and 200 mg doses of lasmiditan.

Results from the 2,232-patient SAMURAI trial, which studied the 100 mg and 200 mg doses of lasmiditan versus placebo, were reported at the American Headache Society meeting in June.

KEEPING A MOSTLY COMPETITIVE POSITION

A second half of 2018 new drug application (NDA) submission to the FDA puts lasmiditan about a year behind Lilly's galcanezumab, for which the company plans to submit a biologic license application (BLA) in the second half of 2017. *(Also see "Lilly Breathing Down Amgen/Novartis's Necks With Three Phase III Migraine Wins" Scrip, 12 May, 2017.)*

Lilly is in at least second place in the race to get the first CGRP inhibitor on the market for the prevention of episodic and chronic migraine headaches, defined as 5 to 14 headache days per month and 15 or more headache days per month, respectively. **Amgen Inc.**'s and **Novartis AG**'s BLA for *Aimovig* (erenumab) has been accepted for the FDA review with a May 17, 2018 PDUFA date.

However, Lilly may be the first on the market with a new and novel oral therapy for the acute treatment of migraines. *(Also see "Best-In-Class Or First-In-Class: CGRP Inhibitors Line Up To Win The Migraine Market" Scrip, 8 May, 2017.)* The rescue medication for use as needed when a headache strikes could fill the gap for patients treated prophylactically with CGRP inhibitors like galcanezumab, which cut monthly headaches days by about one-half to one-third.

Allergan PLC will report results for its oral CGRP inhibitor ubrogepant in the acute treatment of migraine headaches during the first half of 2018 – just months before Lilly's NDA filing for lasmiditan. *(Also see "Allergan Focuses On Aesthetics As Sales Dip For Dry Eye Leader Restasis" Scrip, 4 Aug, 2017.)* **Biohaven Pharmaceuticals Holding Co. Ltd.** is also testing the oral CGRP inhibitor rimegepant as an acute migraine therapy, but while the company only recently began the second of its two Phase III studies, Biohaven expects to report top-line results during the first quarter of 2018. *(Also see "Pipeline Watch: Phase II Readouts With SPK-8011, Velusetrag, GBR-830" Scrip, 4 Aug, 2017.)*

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CNS Licensing Trends: Volume Falls, Values Rise

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Licensing deals involving drugs for central nervous system conditions were worth more in 2016 than previous years, although there are fewer agreements being signed in this disease space. One of the most lucrative CNS pacts since 2012 was **AbbVie Inc.** and Google-funded start-up **Calico Life Sciences LLC's** arrangement for new treatments targeting Alzheimer's and other diseases related to aging.

According to new research from Datamonitor Healthcare, from 2012 through 2015 the total potential deal value for CNS therapies each year was relatively stable at around $2bn to $4bn (this figure includes all known possible milestone payments, but excludes royalties). In 2016 that figure surged to more than $12bn.

Meanwhile, the total number of CNS related alliances has dropped from 23 in 2012 to just 18 in 2016. When looking at all pharma alliances in a year, CNS deals represented 17.2% of deals in 2012 but only 11.3% of agreements signed in 2016 – this is despite the number of total pharma alliances having increased year-on-year since 2013.

"This is not necessarily a reflection of reduced interest in CNS therapies from asset buyers," Datamonitor Healthcare analysts noted. "The drop coincides with the increased availability of both public and private capital for biotechs in general. Thus, companies developing CNS therapies may have more options when it comes to financing the development of their assets."

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With other routes available to biotech companies looking to finance development of new therapies in-house, some might eschew partnerships in favor of retaining greater value, analysts said. Biotech firms were the most active licensers of CNS therapeutic assets during the 2012 to 2016 time period, with 69 alliances in total.

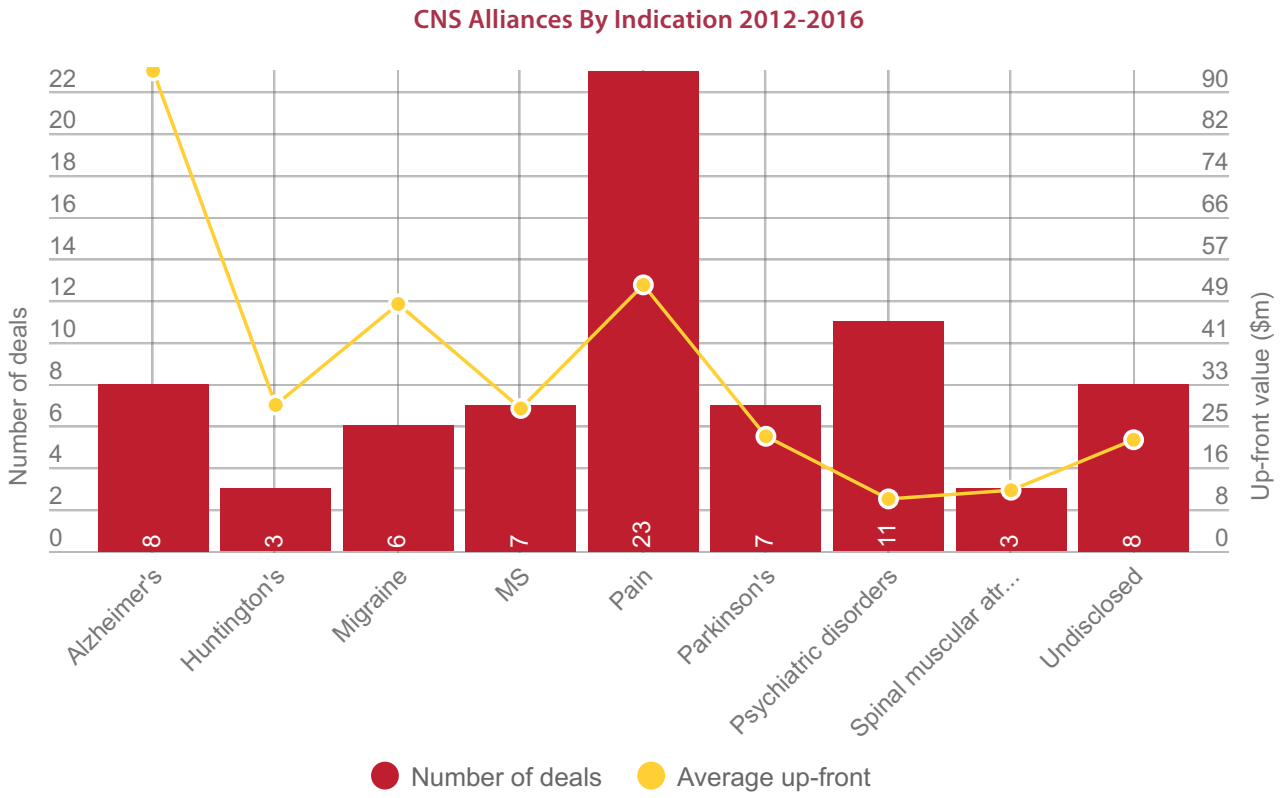
Datamonitor analysts also highlighted in a recent report, titled *Trends in CNS Company Dealmaking,* that alliances around CNS therapeutics were not concentrated in any particular area of the development value chain. "Though there was a slight dip in Phase I and Phase III deals, and a slight peak in Phase II, there was a relatively even distribution from discovery through Phase III," they said.

Last year alone saw some of the biggest CNS alliances based on upfront values. The April 2016 deal between **Allergan PLC** and **Heptares Therapeutics Ltd.** (a division of **Sosei Group Corp.**) could be worth more than $3.3bn as the partners develop selective small-molecule muscarinic receptor agonists from Heptares' pipeline for Alzheimer's disease and related neurological diseases, the most advanced of which are

Top 10 CNS Alliances By Upfront Value 2012-2016

DEAL DATE	LICENSEE	LICENSER	THERAPEUTIC FOCUS	DEVELOPMENT STAGE	UPFRONT VALUE ($M)
June 2016	Aspen Pharmacare Holdings Ltd.	AstraZeneca PLC	Pain	Market	520
Sept. 2014	AbbVie	Calico	Diseases of aging	Discovery	500
Sept. 2016	Teva	Regeneron	Pain	Phase III	250
July 2015	Allergan	Merck & Co	Migraine	Phase II	250
April 2016	Allergan	Heptares	Alzheimer's disease	Phase I	225
Jan. 2014	Jazz Pharmaceuticals PLC	Aerial BioPharma LLC	Narcolepsy	Phase II	125
Aug. 2014	Daiichi Sankyo Co. Ltd.	Charleston Laboratories Inc.	Pain	Phase III	100
Sept. 2013	Biogen Inc.	Ionis Pharmaceuticals Inc.	Amyotrophic lateral sclerosis	Discovery	100
Feb. 2015	Genzyme Corp. (Sanofi)	Voyager Therapeutics Inc.	Parkinson's disease	Phase I	95
Aug. 2014	Allergan	Taris Biomedical LLC	Pain	Phase II	67.5

Source: Strategic Transactions



in Phase I. Allergan paid $125m upfront and the deal includes $2.5bn in potential sales milestones across multiple potential therapies. *(Also see "Allergan 'Unusual Suspect' But Pipeline 'Hunger' A Perfect Match For Heptares" Scrip, 8 Apr, 2016.)*

Furthermore, in September 2016, **Teva Pharmaceutical Industries Ltd.** and **Regeneron Pharmaceuticals Inc.** struck a deal for the latter's Phase III anti-nerve growth factor (NGF) antibody fasinumab for osteoarthritis pain and chronic low back pain that could be worth more than $3.6bn. Teva paid $250m upfront and could pay $460m in development and regulatory milestones, as well as up to $1.9bn in sales milestones. *(Also see "Regeneron Partners NGF Antibody With Teva To Mitigate Risks" Scrip, 20 Sep, 2016.)*

ALLERGAN BUILDING CNS PIPELINE

Allergan has been one of the most active dealmakers in the CNS drug development space in recent years. Since 2012 the company has brought several CNS drugs into its development pipeline and has been the licensee in some of the highest deals by upfront value *(see table)*.

In 2015, marking the most expensive of its recent CNS deals, Allergan paid $250m upfront for **Merck & Co. Inc.'s** investigational small molecule oral calcitonin gene-related peptide (CGRP) receptor antagonists, which are being developed for the treatment and prevention of migraine. Allergan is fully responsible for development of the CGRP programs, as well as manufacturing and commercialization upon approval and launch of the products.

The deal with Merck covers two compounds: ubrogepant, which is now in Phase III development in the US with a pivotal study due to start in Europe by the end of the year; and atogepant, for which Phase II topline data are expected in the first half of 2018.

ALZHEIMER'S DEALS PRICIER UPFRONT

Between 2012 and 2016, pharma and biotech companies agreed more alliances in pain than any other CNS disease area. However, deals for Alzheimer's disease therapeutic candidates captured the highest average upfront deal value of all therapeutic categories. There were eight alliances for Alzheimer's disease therapies during this timeframe, with Allergan/Heptares and AbbVie/Calico leading the way in terms of valuation.

California Life Sciences (Calico) is a Google-founded R&D company led by Arthur Levinson, former chair and CEO of **Genentech Inc.**, and Hal Barron, former executive vice president and chief medical officer of Genentech. Together with AbbVie the startup is focused on developing new therapies for patients with age-related diseases, such as Alzheimer's.

Total number of CNS related alliances has dropped from 23 in 2012 to 18 in 2016

Meanwhile, Allergan acquired the rights to Heptares' portfolio of novel subtype-selective muscarinic receptor agonists in development for the treatment of major neurological disorders, including Alzheimer's disease. Compounds included in this deal are HTL9936, which is in development outside of the US for Alzheimer's and schizophrenia, and HTL18318, which is in US Phase I trials for Alzheimer's.

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[Editor's note: Click here to find more about Datamonitor Healthcare and trend reports.*]*

Pfizer Still Bullish On China

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The China market outlook remains positive for **Pfizer Inc.**, and will continue to bring growth to business with few newly launched products in the country where recent regulations are encouraging multinationals to bring in more novel drugs, although the company's country lead for Innovative Health resigned in the second quarter.

Pfizer's second quarter figures regarding China market were once again a growth hotspot amid stagnant global sales. As Pfizer's largest emerging market, China contributed 45% of total emerging market sales, with 13% growth for the quarter and 16% year-over-year (YoY) for the full six-month period, strengthening from 11% YoY growth for last year.

> Pfizer's second quarter figures regarding China market were once again a growth hotspot amid stagnant global sales

Particularly the Essential Health portfolio that comprise off-patent legacy brands remains a great fit with priority areas of treatment for the Chinese government, including cardiovascular disease, treatments of serious infection and other noncommunicable diseases, according to John Young, Pfizer's group president of Essential Health.

China updated the National Reimbursement Drug List (NRDL) covered by national medical insurance at the end of February this year, the first overhaul since 2009. Pfizer's two exclusive products, *Caduet* (amlodipine besylate and atorvastatin calcium tablets) and *Idamycin* (idarubicin hydrochloride for injection), were included into the list. The update to the NRDL has evidently taken time to impact the market after the inclusion in the first quarter.

NEW PRODUCT LAUNCH HIGHLIGHTS

Pfizer's Innovative Health segment also made progress in China with two new product launches, as China has been making efforts to accelerate approvals of new medicines.

Despite the decrease in global *Prevnar 13* revenues, in international markets, Pfizer reported that Prevnar 13 revenues increased 8% operationally due to the favorable timing of government purchases for the pediatric indication in certain emerging markets.

Through priority review pathway, Prevnar 13 was officially launched in China on April 15 - it took less than six months after its approval by China FDA. It is used for active immunization for the prevention of invasive disease, including bacteremic pneumonia, meningitis, septicemia, and bacteremia in infants and children aged 6 weeks to 15 months.

Currently Prevnar 13 is the only pneumococcal 13-valent conjugate vaccine approved in China, and vaccination has been rolled out in few cities already, such as Kunming, Shenyang, Xi'an, Fuzhou and Nanjing under the National Immunization Scheme. In future, more cities will be added to the scheme.

Another milestone market approval in China is oral Janus kinase (JAK) inhibitor, *Xeljanz* (tofacitinib citrate), for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). The introduction of the first oral JAK inhibitor for RA provides a new option for physicians and adult patients in China where the RA patients number reached around five million.

EXECUTIVE CHANGE

After one year of taking the post as China Lead for Pfizer Innovative Health, Guohong Shan resigned from the company in May. On May 22, Pfizer announced a person temporarily in charge, Kun Wu, who was the general manger for Essential Health in China. The company also said it is open to recruiting a new China lead for Innovative Health, and Wu will remain in the temporary position until the end of this year.

Shan was responsible for internal medicine, inflammation, immunology, oncology, rare disease, and vaccine business in China. And he helped release *Inlyta* (axitinib) in the Chinese market within 86 days and made China the second biggest market for *Xalkori* (crizotinib).

Pfizer remains confident about China. "Just in terms of how we think about China, it has an increasing population, rising personal wealth, higher spending on health care that's a government, public objective, and continues to have a strong GDP so when we look at China, we remain very bullish and the results there have been very strong," said Frank D'Amelio, Pfizer's chief financial officer and executive vice president of business operations.

"We actually think we are very well placed to continue to grow our business in China. It's a major market where we have invested in the past, and we will continue to be opportunistic in making investments in order to drive our business," Young echoed.

In June at the provincial congress of party representatives with multinationals in Hubei, head of Pfizer Wuhan R&D Center told the press that Pfizer China will strengthen its local development capabilities and upgrade technology systems, together with local biopharmas to create a world-class R&D platform in Hubei.

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From the editors of PharmAsia News

Adapting To Changing China Regulations Propels Sanofi But How Far?

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Shutterstock: Digital Deliverance

Sanofi has had a solid quarter in China, driven by its rebounding vaccines business. The French drug maker's sales were up by 17%, returning to high double-digit growth.

The strength comes mainly from vaccines sales, especially its five-in-one vaccine *Pentaxim*, which reported "very strong" growth.

"Growth in our pediatric vaccines of 31% at CER and constant structure reflects strong in-market performance in Europe and China, especially from our AcXim family of pediatrics combination products," said CEO Olivier Brandicourt in the company's second quarter earnings call.

RECONSTRUCT DISTRIBUTION

Shedding more light on the performance, a spokesperson at Sanofi China attributed the growth to adapting to regulatory changes and establishing a new business model, along with increasing demand.

A vaccines distribution freeze was implemented in 2016 when a mother-daughter team in Jinan, Shandong province was found to have distributed vaccines for over a decade, selling them across the country despite possessing no temperature-controlled facilities,

In the aftermath, the government issued a regulation, ordering the distribution of all vaccines to stop, "posing a great challenge for the delivery and transportation of vaccines", said the company.

Since then, Sanofi's vaccine subsidiary Sanofi Pasteur has sought to reconstruct its channels. The company "adopted new logistics solution in a short period of time, and succeeded in establishing a new business model and distribution system to ensure the timely supply of vaccines to the people in need."

Not only timeliness but stricter requirement for temperature controlling required for both domestic and international players were implemented. After the scandal, safety and smooth transfer are increasingly the top issues, said industry insiders. They are required to store vaccines between 2C to 8C throughout the logistic chains, and constant temperature collection is a must because manufacturers are required by China FDA to keep records.

To that end, Sanofi has resorted to a digital tracing system, using technology by Alibaba's health wing, AliHealth.

Meanwhile, China has seen a growing demand for class-two vaccines for pediatric use. That presents opportunities for combination vaccines.

"This [the demand for pediatric vaccines] is leading to greater requirements for the safety and convenience of vaccines. With its advantages, Pentaxim has been widely recognized by parents. As Pentaxim can complement China EPI [essential program for immunization] as well, market demand has grown greatly." said the company.

Helped by the strong demand and quick logistics re-buildup, Sanofi's overall polio/pertussis/HiB vaccines of which Pentaxim is a part grew by 26.3% in emerging markets.

NEW REIMBURSEMENT, PRODUCT LAUNCH

In a bid to provide access to high-priced innovative new drugs to patients, the Chinese government recently offered coverage to 44 medicines with large price cuts.

Among those is *Renagel / Renvela* (sevelamer) from Sanofi, with an indication for hyperphosphatemia among adults with chronic kidney diseases (CKD) in China. The treatment is now covered at CNY243 for a bottle of 30 80mg tablets, a reduction of 35.8% from CNY378.

Overall emerging markets sales are €10m while in China the occurrence rate for audit CKD patients on dialysis is roughly 0.1%, or 700,00 people, said the company.

In May, the Shanghai-based Sanofi China also launched a Genzyme rare disease treatment, *Myozyme* (alglucosidase alfa) in the market. Indicated for Pompe disease, a rare disease estimated to affect two out of 100,000 people in China, the product sales amounted to €33m in the quarter, up 23%.

Despite the estimated rare disease patient population, China hasn't had national financial aid and incentives for orphan drug development, posing challenges to such drugs in the country. Local government such as Shanghai meanwhile has set up its first special fund for lysosomal storage diseases including Gaucher disease and Pompe disease.

Still, Sanofi's biggest selling drug, *Lantus* (insulin glargine) seems to be slowing down in emerging markets in the quarter, after a double-digit decline in the US market. The long-lasting insulin grew 5.5% in the quarter, compared to 9.6% for the first three months.

The group's emerging market sales is €2.6bn for the quarter and €5.17bn in the 1H.

The company's total sales increased by 2.4% in emerging markets in 2016 to €9.59bn and less than 1% in China to €2.04bn in the 12 months.

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From the editors of PharmAsia News

Dermira Takes Roche's Lebrikizumab With Best-In-Class Ambitions

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Medical dermatology specialist **Dermira Inc.** plans to refocus development of the interleukin-13 inhibitor lebrikizumab on the treatment of atopic dermatitis after taking control of the program from **Roche**. Despite growing competition in the therapy area, Dermira sees an opportunity for lebrikizumab to become a best-in-class agent, with potential efficacy and dosing convenience benefits.

The company announced on Aug. 8 that it signed a licensing deal with Roche to gain worldwide rights to develop and commercialize lebrikizumab in all indications outside of interstitial lung diseases such as idiopathic pulmonary fibrosis. Roche has been focusing its development of lebrikizumab on respiratory diseases, but reported mixed Phase III data in asthma patients last year.

Dermira will pay Roche $80m upfront and another $55m in 2018. The company will also pay milestones including $40m upon the initiation of the first Phase III clinical trial and $210m upon the achievement of regulatory and first commercial sale milestones in certain territories. The agreement also includes sales milestones of up to $1.025bn based on the achievement of certain sales thresholds.

Dermira has its eye on the opportunity for the IL-13 inhibitor in atopic dermatitis, a therapy area that is forecasted to become a multi-billion-dollar drug category, albeit a competitive one. The company cited market research forecasting the atopic dermatitis drug market will reach $6bn in 2022.

MULTIPLE BLOCKBUSTERS?

"We believe that moderate-to-severe atopic dermatitis represents one of the largest opportunities in medical dermatology, with seven million patients suffering in the US alone," CEO Tom Wiggans said in a same-day conference call with investors.

"Although there have been some recent advances in the treatment of atopic dermatitis, there remains the need for new therapies that will bring new benefits to patients," he said. "We believe the atopic dermatitis market can likely sustain multiple blockbuster products over time as new differentiated treatments are introduced."

Dermira plans to initiate a Phase IIb dose-ranging study testing lebrikizumab in adult patients with moderate-to-severe atopic dermatitis in the first quarter of 2018 to find the optimal dose to move into Phase III trials. Roche has already demonstrated proof of concept for the drug in atopic dermatitis in a Phase II study, TREBLE, that enrolled 209 patients.

Dermira wants to evaluate a loading dose and higher dose regimens than were studied previously by Roche.

Chief development officer Luis Pena said the drug has shown an opportunity to achieve high levels of extended coverage, which could result in increased efficacy and dosing advantages.

Those advantages could give lebrikizumab an edge in a competitive market. Partners **Regeneron Pharmaceuticals Inc.** and **Sanofi** recently launched the first biologic treatment for atopic dermatitis earlier this year, *Dupixent* (dupilumab), which has gotten a lot of attention for being the first drug to treat the disease systemically. Dupixent, an IL-4 receptor antagonist, works through a different mechanism of action, than lebrikizumab. Other rivals are also targeting the therapy area.

"We believe the unmet patient need will remain significant even in the context of new launches," chief commercial officer Lori Lyons-Williams said.

"Even in a market that assumes multiple new entrants in the years to come, if one assumes a similar safety profile and comparable efficacy results to dupilumab, it's clear that lebrikizumab, with a less frequent and therefore more convenient dosing schedule, has the potential to become a blockbuster," she said. "If we are able to also demonstrate a best-in-class efficacy profile paired with an extended dosing schedule, the market opportunity could present even further upside for lebrikizumab."

Dermira believes it would have cash and equivalents sufficient to meet requirements into the first half of 2019 if the deal closes in the third quarter as expected. The company received net proceeds of $278.2m after completing a private placement fundraising in May and had cash of $695.9m as of June 30.

MEDICAL DERMATOLOGY NICHE

The Menlo Park, Calif. company is emerging as a serious contender in the niche market of medical dermatology.

"Dermira's late-stage dermatology portfolio looks fairly unique for a company this size," Evercore ISI analyst Umer Raffat said in a same-day note to investors.

Wiggans talked about the company's ambitions to lead in medical dermatology during the conference call. "When the company was founded seven years ago, it was with the view there was a unique opportunity in a field with a highly underserved patient population, a group of dermatologists and health care providers committed to their care, and exciting new science that could lead to important new therapies," Wiggans said. "We believe what was true then is still true today."

The company has a near-term commercial opportunity horizon with *Cimzia* (certolizumab) for the treatment of moderate-to-severe chronic plaque psoriasis. Dermira led the development of the **UCB Group**-owned anti-TNF for psoriasis under a 2014 agreement. Dermira gained the rights to develop and commercialize Cimzia for dermatology indications in the US and Canada, while UCB held onto rights to commercialize in Europe The companies reported positive Phase III data from three trials earlier this year and filed a supplemental BLA with the US FDA.

The company has made progress on other fronts as well. It is on track to submit an NDA to the FDA for glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis in the second half of 2017, and plans to complete enrollment in two Phase III trials testing olumacostat glasaretil in patients with acne vulgaris in the fourth quarter.

"We have successfully advanced three programs through or into Phase III in the last 18 months," Wiggans noted.

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Valeant Sees Sunshine On Cloudy Day, But Dermatology Recovery Just Starting

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Valeant Pharmaceuticals International Inc. executives strived to accentuate the positive during a second quarter earnings call on Aug. 8 and investors didn't completely reject the argument, as the troubled company's stock closed the trading day up nearly 2%. However, to buy into the good news, one must accept Valeant's assurances that it can turn around a struggling dermatology franchise and that ahead-of-schedule debt reduction efforts will enable it to regain overall footing before a heavy debt crunch in 2020-21.

CEO Joseph Papa characterized Valeant's path to recovery from a mountain of debt, legal troubles and patent expirations as one in which stabilization occurred last year and recovery is underway this year and next. *(Also see "Debt-laden Valeant Sells Its Assets, More Divestments Likely" Scrip, 10 Jan, 2017.)* Much of the firm's argument was that revenues for its eye care and gastrointestinal businesses are on the rise – if one discounts the impact of foreign exchange and debt-reducing divestitures, he and chief financial officer Paul Herendeen explained.

"We have a journey ahead of us to be clear," Papa told the same-day conference call. "It's going to be a multi-year process to transform this company, but I am very pleased with the progress that our team has made so far. We completed the stabilization phase in year one, and we are now on the early part of a two-year turnaround phase, where our focus is on strengthening our balance sheet, maintaining leadership positions in specialty-driven markets and those markets with above-average growth rates, and allocating resources efficiently."

For the quarter, Valeant reported revenues of $2.33bn and a net loss of $38m compared to the second quarter of 2016. However, the **Bausch & Lomb Inc.** (B&L) ophthalmology and **Salix Pharmaceuticals Ltd.** GI units delivered what Valeant is calling "strong organic growth," which Herendeen defined as adjusting reported revenue to negate the impact of foreign exchange rates over 12 months and the loss of revenue from divested assets. In that light, the two units, which together accounted for 73% of the company's quarterly revenue, were up 6% and 16%, respectively, year-over-year.

Salix's 16% organic growth exceeds the unit's 13% overall growth during second-quarter 2017, Valeant stated, while B&L was down 3% overall but up 6% organically. Leading the way for the GI business was the irritable bowel syndrome stalwart *Xifaxan* (rifaximin) – with 16% sales growth and improving prescriptions trends, up 6% sequentially and 2% year-over-year. B&L was bolstered by 4% growth in China, or 9% on an organic basis. Papa said B&L currently accounts for 56% of Valeant's total revenue.

EXCLUSIVITY LOSSES

Another headwind for Valeant has been exclusivity losses across its various business segments, Herendeen noted. Combined with revenue lost to divested business units and products, Valeant projects it will lose a net $675m in revenue this year, including anticipated patent expiries in its ophthalmology (*Lotemax* (loteprednol etabonate), *Istalol* (timolol maleate)) and branded Rx (*Mephyton* (phytoniadone), *Syprine* (trientine), *Isuprel* (isoproterenol)) segments.

"The bolus of LOEs hitting the company in the 2016 and 2017 timeframe is quite large and creates a growth drag that we cannot overcome," he said. "The decline in the LOE products reduced revenue by some $110m and pre-tax profits by roughly $100m in the quarter compared with Q2 of 2016."

Sales growth for B&L derived 2% from price increases and 4% from volume growth, Herendeen said. International business drove the growth, increasing 17%, with emerging markets such as Russia, China, Mexico, the Middle East and certain African countries leading the way.

One setback for ophthalmology was a second complete response letter regarding Valeant's US NDA for *Vyzulta* (latanoprostene bunod), a single-agent eye drop for open-angle glaucoma or ocular hypertension. Valeant disclosed the CRL – the second for this candidate – on Aug. 8 and said that like the first, it was related to the FDA concerns about manufacturing processes at a plant in Tampa. *(Also see "Keeping Track: Approval Elusive For Biosimilar Neulasta; Valeant Gets A Nod And A No From FDA; Submissions From Amgen, Puma, Bristol" Scrip, 22 Jul, 2016.)* Papa called the letter disappointing news and said Valeant will work with the FDA to resolve the manufacturing issues.

INCREASED XIFAXAN DEMAND

Branded prescription product business decreased 3% overall and basically was flat on an organic basis, he added. But Salix provided reason for optimism, thanks largely to increased demand for Xifaxan, the exec noted. Overall Salix sales volume increased 350 basis points, with investments in a new primary care sales team bringing results, he said.

"We enjoyed improved net pricing in the Salix business as result of modest price increases across the GI portfolio as well as favorable gross-to-net items compared with the prior year quarter. While the improved net pricing is awesome, I just caution that part of that improvement is less durable than the rest," Herendeen cautioned. But he was less reticent about Xifaxan's growth prospects.

"In Q2 compared with Q2 last year, total prescriptions for Xifaxan were up 2%," he noted. "After we lost some momentum with Xifaxan in late 2016 and into Q1 of 2017, it's encouraging to have our most recent results showing a return to growth." Elsewhere in the GI portfolio, *Apriso* (mesalamine) prescriptions increased 7% while *Relistor* (methylnaltrexone bromide) scripts shot up 33% year-over-year.

Herendeen made no effort, however, to paint a bright picture of the dermatology franchise, noting that filled prescriptions declined during the second quarter from what had been a soft first quarter. Overall, dermatology revenue tumbled 31% from the second quarter of 2016.

CONTINUED ON PAGE 23

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

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

Selected clinical trial developments for the week 4–10 August 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Interim/Top-line Results			
Durect Corp.	*Oradur* methylphenidate ER capsule	attention deficit hyperactivity disorder	A Phase III study in Taiwan, found safe and effective.
Starpharma Holdings Ltd.	*ViVaGel* (astodrimer sodium)	bacterial vaginosis	Prevention of recurrent infections observed.
Eli Lilly & Co.	lasmiditan	acute migraine	SPARTAN; met primary endpoint in second Phase III study.
Phase III Initiated			
Rebiotix Inc.	RBX2660 (spore and non-spore microbes)	recurrent *C difficile* infection prevention	Delivered into the GI tract.
Bayer AG	vilaprisan	uterine fibroids	ASTEROID 5; in nearly 1,000 subjects.
CytoDyn Inc.	PRO 140, an antibody against CCR5	HIV infection	Combined with antiretroviral therapy.
Mithra Pharmaceuticals SA	*Estelle* (estetrol plus drospirenone)	contraception	A pharmacokinetic substudy.
Motif Bio PLC	iclaprim	skin & skin structure infections	REVIVE-2; dosing completed.
Evofem Holdings Inc.	*Amphora* (L-lactic acid, citric acid, and potassium bitartrate)	contraception	A vaginal gel.
Phase III Announced			
Akebia Therapeutics Inc.	vadadustat	anemia in chronic renal failure	TRILO2GY; in dialysis dependent patients.
Helsinn Group	*Monofer* (iron isomaltoside)	iron-deficiency anemia	Versus other iron preparations.
Phase II Suspended			
Zynerba Pharmaceuticals Inc.	ZYN002 (transdermal cannabidiol)	focal seizures in epilepsy	STAR 1; missed primary endpoint, results from other studies awaited.
Updated Phase II Results			
Corbus Pharmaceuticals Holdings Inc.	resunab (a synthetic endocannabinoid mimetic)	scleroderma	Improved fibrosis and inflammation.
Allegro Ophthalmics LLC/Hanmi Pharmaceutical Co. Ltd.	*Luminate* (ALG 1001)	diabetic macular edema	DEL Mar; visual acuity gains reported with this anti-integrin oligopeptide.
Bonti Inc.	EB-001 (a novel serotype E botulinum toxin)	glabellar lines	Favorable safety and shown to be a fast-onset, short duration (4 weeks) neurotoxin.
Galapagos NV	GLPG1690	idiopathic pulmonary fibrosis	FLORA; well tolerated, signs of efficacy.

Source: Biomedtracker

CONTINUED FROM PAGE 21

"The dynamics of the dermatology segment have been changing over the last several years with payers more aggressively restricting access to branded products" he explained. "Layer on top of that the challenges we face in converting from a specialty pharmacy-based model in early 2016, and we simply have not been able to deliver to our own or likely to your expectations. We take full responsibility for that."

To address those issues, Herendeen pointed out that the dermatology sales force had been "right-sized" from a headcount of 250 to 151, while the company invested in sales support systems and market access. The goal is to bring dermatology back to a growth trajectory via improved execution with its existing product portfolio and the successful launch of new products. Later during the call, Papa said he anticipates that recently launched *Siliq* (brodalumab) will be a "new growth driver" for this business, although analysts have questioned the sales potential of the IL-17 blocker for psoriasis. *(Also see "Siliq Probably Isn't The Light At The End Of Valeant's Tunnel" Scrip, 28 Feb, 2017.)*

Asserting that the dermatology business is stabilizing, Papa also said he's gotten positive feedback from clinicians about the therapeutic utility of Siliq, which was priced lower than competing psoriasis drugs. *(Also see "Valeant Gives Siliq Competitive Price In Crowded Psoriasis Market" Scrip, 21 Apr, 2017.)* "I spent some time with key opinion new leaders at a product launch of that last week, and I was strongly encouraged by their enthusiasm for Siliq's unique method of action and strong efficacy," he said. "We are leveraging these key opinion leaders to educate and activate patients who can benefit from the pharmacologic properties of an IL-17 blocker."

Papa reiterated Valeant's intention to reduce its debt, noting that 10 of 12 announced divestitures over the past year have closed, while the more recent sales of **iNova Pharmaceuticals Pty. Ltd.** and **Obagi Medical Products Inc.** are expected to close before the end of 2017. *(Also see "Deal Watch: Valeant Continues Divestment Spree By Selling Obagi At A Loss" Scrip, 25 Jul, 2017.)* As of Aug. 15, Valeant will have reduced its debt by $4.8bn, putting it ahead of schedule to cut $5bn in debt as of February 2018, the exec noted. *(Also see "Valeant On Track With Debt-Reduction Goals, But Will It Be Enough?" Scrip, 9 May, 2017.)* Herendeen said the efforts to date give Valeant near-term flexibility to grow its business as it now will not face significant debt maturities until 2020-21.

Valeant closed trading on Aug. 8 up 2% to $15.63 per share, continuing a recent trend of price appreciation. Analysts, not surprisingly, gave Valeant mixed grades for the second quarter, including Douglas Tsao of Barclay's, who lauded the company's debt-reduction progress so far. He maintained an "equal weight/positive" rating for the stock in an Aug. 8 note.

"Valeant's ability to buy time has clearly likely been the biggest driver of recent share strength; to drive meaningful upside, we believe the next leg of the story has to be around driving underlying business performance/sustainability," he said.

Timothy Chiang of BTIG Equity Research said some of the underlying business trends already are pointing in the right direction., "It appears that volume trends for a number of the GI products have improved in 2Q17 versus 1Q17, including Xifaxan, Apriso and Relistor," Chiang said in an Aug. 7 note previewing the earnings call. "With Xifaxan, total prescriptions were up about 6%, sequentially, with year-over-year growth essentially flat in Q2."

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APPOINTMENTS

Novo Nordisk AS has named ***Camilla Sylvest***, its senior vice president heading the company's operations in Region China, executive vice president in charge of commercial strategy and corporate affairs. Sylvest was appointed senior vice president and general manager of Novo Nordisk's Region China in 2015 and started her career at the company in 1996.

Horizon Pharma has appointed ***Pascale Witz*** and ***James Shannon*** to its board of directors. Witz carries over 20 years of experience and most recently, she was executive vice president, global diabetes and cardiovascular at Sanofi. Before this, Witz spent 17 years at GE Healthcare where her final role was president and CEO of its medical diagnostics business. Most recently, Shannon was chief medical officer of GlaxoSmithKline Plc., and previously, he was at Novartis as global head of pharma development.

Hugh Cole has been appointed **Jounce Therapeutics**' chief business officer and head of corporate development. He brings more than 25 years' experience in the biotech industry, with his most recent position at ARIAD Pharmaceuticals, where he was chief business officer. Cole was the former senior vice president strategic planning and program management at Shire Plc., and before this, he was vice president, corporate development for Oscient Pharmaceuticals.

Pfenex Inc., a biotech focused on biosimilar therapeutics, has named ***Evert Schimmelpennink*** CEO and member of its board of directors. Current interim CEO, and secretary, ***Patrick Lucy***, will now continue as chief business officer.

Pharmalink AB has appointed ***Fredrik Johansson*** chief financial officer (CFO) and ***Mikael Widell*** new head of communications. Johansson previously was CFO and chief operating officer at Birdstep Technology/Techstep ASA. Widell was originally a journalist and since 1998, held corporate communications position at various life science companies, including AstraZeneca, Biovitrum and Oasmia.

Curtis Oltmans has joined cancer-focused **Array BioPharma** as general counsel. With mainly legal experience, Oltmans was recently corporate vice president and general counsel, North America, at Novo Nordisk Inc. He also held various legal roles over the 13 years he spent at Eli Lilly & Co.

Takeda Pharmaceutical Co. Ltd. vice president and area head, Greater China, ***Pony Lu*** is leaving, the company confirmed in an e-mail statement. Citing Lu's personal decision to pursue other career opportunities, Takeda said Lu's last day at the company is Sept. 29. The company will be looking for a replacement and expects no material impact to the business. Lu became the area head early this year after former head ***Akira Noguchi*** left the position.

China FDA has appointed ***Sun Meijun*** as deputy commissioner in charge of food safety. Sun started her career at the China Statistics Bureau and later was director of the rural region.

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29 November 2017 | London Hilton on Park Lane

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